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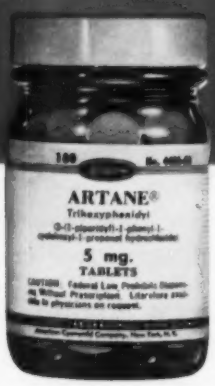

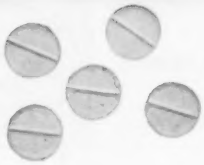

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SPINAL CORD COMPRESSION STUDIES

II. Time Limits for Recovery After Acute Compression in Dogs

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NEW YORK

IT IS CLINICALLY important to determine how long the spinal cord may be compressed without precluding functional recovery, because it would lead to more rational and standardized treatment. One would expect the time to be short because of the vulnerability of nerve tissue to mechanical distortion and anoxia.

Allen* attempted to answer this question by producing contusion of the spinal cord of dogs. His technique was to drop known weights from known heights on the spinal cord. The degree of the impact was measured in gram-centimeters. Allen believed that the edema following the impact reached its maximum about four hours after the injury. He concluded that if the spinal cord compression caused by the edema could be prevented, the spinal cord might recover some function. Accordingly, he advised midline posterior incision of the spinal cord through the contused segment to drain and release the intramedullary pressure. He made such incisions in dogs two hours after injury by a force known to produce complete paralysis. He reported that he could thus avert the disintegration of cord tissue that invariably occurred in the control dogs in which the spinal cord was not incised.

A valid objection to Allen's interpretation of these changes is well expressed by Thompson [12]:

> There is no doubt that the substance of the cord is clearer and better preserved in the incised than in the nonincised specimen but there is such a decrease in transverse area of the cord that we can't help feeling that the diffluent tissue which escaped from the incision carried with it a considerable amount of nervous tissue which had not been seriously injured and which might have been expected reasonably to have recovered if it had not been disturbed. While it lies in the substance of the cord it acts as support to the uninjured tissue surrounding it. Evacuation removes this support and the walls of the cavity cave in like the sides of a sand pit or the banks of a river when the waters recede. On these grounds we believe that the evacuation is not without its drawbacks and its dangers.

Allen's experiments have fallen short, therefore, of solving our problem.

PURPOSE OF INVESTIGATION AND METHOD

In Part I of our present series of studies, we [10] described techniques for producing acute and gradual compression of the spinal cord and cauda equina in dogs. The present report deals with the functional and histologic results of acute com-

From the Department of Neurology and Neurosurgery, New York Medical College. This study was aided by grants from the United States Public Health Service and the Veterans Administration.

* References 1 and 2.

pression of these structures for varying lengths of time. We determined the time limits beyond which recovery of function did not occur. We also attempted to investigate the sequence of loss and recovery of function after spinal cord compression and decompression.

In each case compression was begun after the dog had fully recovered from the operation at which the acute compression device was inserted. An attempt was made to place the balloon exactly in the middle of the epidural space ventral to the spinal cord. This proved difficult because of a midline vertebral ridge, which deflected the balloon ventrolaterally. For spinal cord compression the balloon was placed at the level of T5–T9 vertebrae and was introduced through a small laminectomy at T12. The position of the balloons was checked by x-rays. The balloons were inflated to three sizes. The large-size balloon when fully inflated had approximately the same diameter as the vertebral canal; its capacity was about 1 cc. Complete paralysis followed its inflation in all cases. The capacity of the medium-sized balloon was approximately 0.9 cc. Inflation produced complete paralysis in 90% of the dogs. The small-sized balloon (capacity about 0.8 cc.) was inflated by turning the screw of the compression unit slowly just to the point of complete paralysis and complete loss of sensation.

To compress the cauda equina, the deflated balloon was introduced through a small laminectomy between L7 and S1 vertebrae and passed upward extradurally to the level of the middle of the L5 vertebra. We found that division of the cauda equina nerve roots at this level usually produced paralysis of the lower limbs, which was complete at the ankles and knees but not always complete at the hips. These effects were not produced when the conus medullaris † was divided at this site. Severance of the lower end of the spinal cord at higher levels, however, did produce severe weakness of the lower limbs. The paralysis produced by inflation of the rubber balloon at the fifth lumbar vertebral level is therefore primarily a cauda equina rather than a spinal cord effect. Paralysis produced by inflation of the balloon at a higher lumbar level, however, results from compression of the lower end of the spinal cord, which innervates the lower limbs, as well as from compression of the cauda equina.

Only the large-size balloons were used to compress the cauda equina because the others usually failed to produce paralysis. The fact that the lumbar is larger than the thoracic vertebral canal and the cauda equina roots are more resistant to compression than the spinal cord accounted for the frequent failure of the inflated smaller balloons to paralyze the hindlimbs.‡

We started using medium-sized dogs in our experiments to minimize variations in diameter of the vertebral canal. The difficulty of procuring dogs, however, forced

† In man the fourth sacral spinal segment marks the beginning of the conus medullaris, as suggested by van Gehuchten and de Neef on the basis of the disappearance of cells innervating the lower limbs at this level. In dogs the conus appears to begin under the fifth lumbar vertebra, since its severance at this level does not as a rule produce weakness of the lower limbs.

‡ We examined directly the reaction of the balloon to inflation in an isolated segment of the vertebral column and spinal cord. The balloon was placed in the vertebral canal equidistant from the ends of a given vertebra. When inflated, the balloon migrated upward or downward to the intervertebral disc space, which is roomier than the space lying strictly within the vertebra. This phenomenon probably explains the variation in results of cauda equina compression. The extent of the paralysis is less when the balloon migrates to the lower, rather than to the upper, intervertebral space.

us to compromise our plan and use some dogs that were almost twice the size of others. Consequently, partial, rather than complete, paralysis occasionally followed inflation of the balloons. These partially paralyzed dogs were included in a separate series.

During acute compression of the spinal cord or cauda equina in the unanesthetized dog the loss of function appeared suddenly and usually disturbed all forms of sensation and motor power simultaneously. The compression was maintained for varying lengths of time. The balloon was then deflated and the spinal cord or cauda equina thus decompressed. The metallic compression device was removed a day or two after decompression, but the balloon was left in place. Control animals in which balloons were kept in the thoracic and lumbar vertebral canals for as long as one year have shown no abnormal neurologic signs.

During compression of the spinal cord or cauda equina it was occasionally noted that an animal lost all motor power of the hindlimbs but retained pain sensation. In one such animal rapid recovery followed a relatively long period of compression. It was therefore decided to study a group of dogs in which thoracic compression was carefully applied to a point where motion of the hindlimbs was lost but where pinprick appreciation was clearly retained. Pain sensation was indicated by growling, head turning toward the stimulus, or attempts to withdraw from it. In most of these dogs the paralysis which was complete at the ankles and incomplete at the knees and hips immediately after compression became quite complete at these joints 24 hours later, when pinprick sensation of the paws often disappeared.

Immediately after decompression all dogs were tested at frequent intervals during the day. Later the intervals were increased to daily, semiweekly, or weekly, depending on the rate of functional recovery.

The criteria which we have used for studying the recovery of motor function of the hindlimbs follow: 0, no voluntary movement; 1, perceptible movement at joints; 2, good movement at joints but inability to stand; 3, ability to stand and walk, and 4, complete recovery.

Pain sensibility was tested by observing the withdrawal reaction of the foot or the body or repeated turning of the head in the direction of successive pinpricks applied to the plantar surface of the paw. There is considerable variation in the response of normal dogs to pinprick, so that the evaluation of pain sensibility is difficult in some animals. Position sense was tested by observing the ability of the animal to correct an upside-down position of the foot. Touch sensation was determined by thrusting the animal's foot over the edge of the table to see whether the foot would be returned to its original position.[11] This is the placing reaction described by Rademaker. Both touch and position sense are dependent upon good motor power of the limbs; otherwise, these sensations cannot be tested.

The dogs were killed when they had fully recovered or when a stationary course had been maintained for a long time. Some of the dogs died before reaching such a stage.

At autopsy the vertebral column containing the spinal cord was carefully removed at the site of cord compression and for several segments above and below it. After the spinal cord was well fixed in formalin, it was removed from the vertebral column. Three 5-mm. sections of the spinal cord were excised at the compression site and also at various levels above and below it. These were fixed in formalin. One series of these blocks was then embedded in paraffin for hema-

toxylin-eosin stains and Gros-Bielschowsky preparations for axis cylinders. Another set of sections was embedded in celloidin, cut, and stained for myelin sheaths by the Weigert-Pal technique. Sections were cut on the freezing microtome from the third set of blocks and stained for fat with scarlet red.

RESULTS

A. Functional.—When the spinal cord or cauda equina is compressed, the dogs immediately become restless, growl, and sometimes urinate, defecate, and attempt to bite. It is difficult to follow the sequence of loss of function because of the sudden onset of the paralysis. Tests for position sense and touch sense are both dependent on good motor power of the limbs, so that paralysis precludes such tests. We have often observed, however, that a dog may show complete hindlimb paralysis and yet feel pinprick applied to the plantar surface of the paws of these limbs. This is indicated by his head turning to the site of the pinprick, by his attempt to withdraw, or by barking. Dog 10 showed this kind of persistent pain response after complete paralysis of the hindlimbs occurred. In all dogs listed in Tables 1 to 4 in which pain sensation persisted after the onset of complete paralysis the balloon was further inflated to the point where pain sensation stopped.

Compression of the spinal cord was usually followed by extensor rigidity of the hindlimbs, and occasionally by transitory extensor rigidity of the upper limbs also. Deep lower limb reflexes remained either normal or increased during paralysis. Flaccid paralysis and loss of deep reflexes of the hindlimbs followed cauda equina compression.

Examination of Tables 1, 2, 3, and 4 shows that whether recovery of the spinal cord and cauda equina occurs after compression depends not only on the duration of the compression but also on its magnitude. At best, however, compression leading to complete paralysis compatible with functional recovery is of very short duration. With great compression (large balloons) full functional recovery occurred after one minute of compression. Recovery was partial after a five-minute period of compression, but no return of function followed longer compression, nor did it occur in those two dogs in which two- and three-minute periods of compression were applied.

The duration of acute spinal cord compression compatible with full functional recovery is markedly prolonged if pinprick sensation remains immediately after compression. Dogs subjected to such compression for as long as one week showed almost full recovery, and considerable recovery occurred in dogs in which the compression period was as long as two and three weeks.

When spinal cord paralysis was produced by forces of less magnitude (medium-size balloons), recovery followed longer compression (Table 2). Complete recovery followed compression for 10, 15, and 30 minutes, but not after 1 hour or longer. One dog recovered completely after 24 hours of compression, but he had shown persistent pinprick appreciation of the lower limbs, indicating that the compression was incomplete.

In another series of spinal cord compressions the balloon was inflated just to the point of complete sensorimotor paralysis but no further (Table 3). These animals recovered completely when compression was maintained for as long as two hours. Recovery did not occur after longer periods of compression.

In these spinal cord compressions causing total sensorimotor paralysis, pain sensation recovered first in five of the six dogs in which full function returned. Motor power and position sense recovered before pain in the sixth dog. We have had clear-cut evidence of the return of pain sensation to the hindlimbs of a dog in which position sense was totally lost.

TABLE 1.—*Acute Spinal Cord Compressions (Large Balloons) with Complete Paralysis*

Dog No.	Duration of Compression	Degree of Paralysis at Time of Sacrifice	Compression Site	Interval, in Days from Compression to Recovery or Sacrifice	Histologic Results
28	10 min.	100%	T12	47	Complete destruction of spinal cord at compression site; cavity filled with monocytes and fat-filled phagocytes
29	30 min.	100%	T11	90	Complete destruction of spinal cord at compression site; large phagocytes, some containing fat, in cavity
30	2 hr.	100%	T7	20	Marked rarefactive necrosis of spinal cord at compression site, where moderate numbers of intact axis cylinders are present
31	1 hr.	100%	T8	27	Extensive cavity formation at compression site
32	3 hr.	100%	T10	71	One-half of spinal cord at compression site occupied by cavity, other half being trabeculated; many fat-filled phagocytes, lymphocytes, fibroblasts, and connective tissue fibers present at this site, where few intact nerve fibers are present
34	2 hr.	100%	T8	10	Massive necrosis and hemorrhages at compression site extending from T6-T9, where but few intact axis cylinders are present; this area infiltrated by polymorphonuclear leucocytes and monocytes
35	1½ hr.	100%	T8	11	Almost complete destruction of spinal cord at compression site, where there is a large cavity containing fat-filled phagocytes. Destroyed cord occupies two segments
36	5 hr.	100%	T5	32	Complete destruction of spinal cord at compression site. Cavity contains fat-filled phagocytes
37	4 hr.	100%	T3	11	Trabeculation of spinal cord at compression site, where nerve fibers are markedly reduced in numbers
38	3 min.	100%	T12	23	Complete destruction of spinal cord at compression site, where few nerve fibers are intact
50	1 min.	0%	T8	21 Recovery started in 1-2 days	No histologic abnormality
80F	22 min.	100%	T8	2	Complete destruction of spinal cord at compression site
51	2 min.	100%	T7	180	Almost complete destruction of spinal cord at compression site, where nerve roots however are quite normal
52	5 min.	20%	T7	180 Recovery started in 10-18 days	No abnormality in hematoxylin and eosin stains, but Gros-Bielschowsky preparations show rather marked diminution of nerves at compression site

The onset of recovery and its completion were most rapid in dogs in which compression periods were shortest. For example, motor recovery began from two to three days after a 10-minute spinal cord compression with the medium-size balloon. Recovery of function was complete in the four dogs of this series in which 10-minute compression was used. On the other hand, one animal (Dog 46) in

TABLE 2.—*Acute Spinal Cord Compressions (Medium-Sized Balloons) with Complete Paralysis*

Dog No.	Duration of Compression	Degree of Paralysis at Time of Sacrifice	Interval, in Days, from Compression to Recovery or Sacrifice	Compression Site	Histologic Results
10*	24 hr.	0%	45 (Recovery started in 3-5 days)	T8	Small cavity in gray matter and slight vacuolation of white matter at T8; fat-filled phagocytes present in walls of cavity; slight thinning of axones around part of cavity wall
11	48 hr.	100%	16	T7	Large cavity occupying over half of spinal cord at T7 and surrounded by disorganized tissue containing many fat-filled phagocytes; axis cylinders and myelin sheaths rarefied around cavity; these changes present at compression site
15	6 hr.	100%	95	T7	Complete cavitation of spinal cord at compression site except for narrow rim containing some myelinated nerve fibers; many fat-filled phagocytes present within cavity
16	48 hr.	100%	93	T11	Cavity the size of the ventral gray horn present in lateral funiculus and surrounded by glioses and fat-filled phagocytes; ganglion cells at compression site pyknotic; white matter at compression site vacuolated
18	3 hr.	100%	3	T7	Extensive fresh hemorrhage and disruption of spinal cord structure at compression site; hemorrhage extends from T8 to T2
25	36 hr.	100%	4	T7	Central area of softening covering one-fourth the cord area, present at compression site and surrounded by vacuolated tissue
26	12 hr.	100%	94	T7	Complete destruction of spinal cord and intense connective tissue scarring at compression site, where fat-filled phagocytes occur
27	36 hr.	100%	49	T12	Extensive cavitation at compression site; many intact myelinated nerve fibers are present at this level, however
44	15 min.	0%	46 (Recovery started in 15-20 days)	T8	No histologic abnormality
46	30 min.	0%	22 (Recovery started in 15-20 days)	T8	Considerable rarefaction of gray and white matter at compression site; most nerve fibers appear normal at this level, however, in Gros-Bielschowsky and Weigert-Pal preparations
61	1 hr.	75%	17 (Recovery started in 15 days)	T7	Moderate rarefaction of gray and white matter at compression site with considerable decrease of axone density
57	4 hr.	100%	35	T7	Complete cavitation of spinal cord at compression site; many fat-filled phagocytes present
58	3 hr.	100%	32	T7	Moderate rarefaction at compression site, where nerve cells are pyknotic and nerve fibers considerably diminished in numbers
59	2 hr.	100%	33	T7	Large cavitation at compression site; many fat-filled phagocytes occupying cavity; large numbers of myelinated axones present at this level
79	10 min.	0%	8	T7	Slight vacuolation of spinal cord at compression site
81	10 min.	0%	15	T7	Slight vacuolation of spinal cord at compression site
63	5 hr.	100%	180 days	T7	Complete destruction of spinal cord, with fibrous tissue replacement at compression site; fat-filled phagocytes but no intact nerve fibers present at compression site
65	6 hr.	100%	150 days	T7	Complete destruction of spinal cord with fibrous tissue replacement at compression site
70	10 min.	0%	20 (Recovery started in 2-3 days)	T7	No histologic abnormality
72	10 min.	0%	27 (Recovery started in 3-8 days)	T7	No histologic abnormality

* This dog was the only one in this series that showed persistent pinprick appreciation of the lower limb, indicating that the compression was incomplete. This dog therefore belongs in the series of partial compressions.

which the same compressive force was applied for 30 minutes did not begin to show evidence of recovery until 15 to 20 days later, and recovery was not complete until approximately 32 days after compression. The latest onset of recovery was 20 to 30 days after spinal cord compression. This occurred in dogs compressed with small balloons for from 50 to 120 minutes. Recovery was complete in these dogs two to six months after compression.

The dogs in which cauda equina compression was applied followed this same rule; that is, the shorter the period of compression the sooner the beginning and the completion of functional recovery.

TABLE 3.—*Acute Spinal Cord Compressions (Small Balloons) with Complete Paralysis*

Dog No.	Duration of Compression	Degree of Paralysis at Time of Sacrifice	Interval, in Days, from Compression to Recovery or Sacrifice	Compression Site	Histologic Results
74	60 min.	0%	172 (Recovery started in 20-25 days)	T8	Cavity in dorsal gray matter overlapping dorsal horns; normal surrounding axones and myelin sheaths
75	50 min.	0%	161 (Recovery started in 20-30 days; full recovery in 3 mo.)	T8	Cavity occupying gray matter at T7 overlapping white matter; moderate degeneration of surrounding axones and myelin sheaths
76	40 min.	0%	60 (Recovery started in 10-15 days)	T8	Small cavity in dorsal gray matter at T7; normal surrounding axones and myelin sheaths
77	90 min.	0%	54 (Recovery started in 9 days)	T8	No histologic abnormality
78	120 min.	10% (Slight limp)	180 (Recovery started in 15 days)	T8	Slight vacuolation at compression site; normal axones and myelin sheaths
89	45 min.	0%	107 (Recovery started in 13 days)	T8	No histologic abnormality
85	15 min.	0%	180 (Recovery started in 16 days)	T8	Slight vacuolation at compression site; normal axones and myelin sheaths
88	180 min.	100%	37	T8	Histologic study not made

Examination of Table 4 shows that the duration of acute cauda equina compression and paralysis compatible with full functional recovery was longer—five hours with the largest compression forces. However, recovery failed to occur in some of the dogs in which compression was applied for shorter periods to the cauda equina. For example, failure of recovery in one of the two dogs subjected to cauda equina compression for three hours resulted from softening of the spinal cord extending upward a distance of three vertebral arches. In other words, the lesion in this case was myelitic rather than radicular. In Dog 13, subjected to six hours of compression, autopsy revealed the balloon at the level of the third lumbar vertebra. Either the balloon had moved upward after its insertion at operation, or it was misplaced. This dog belongs in the series of spinal cord rather than of cauda equina compressions. Dog 49, subjected also to compression for six hours, failed to recover. A large cavity extended upward from the compression site at L5 to T12 vertebral

level. The anterior horn cell outflow to the sacral plexus was thus completely destroyed. These experiences point up the difficulty in producing consistent cauda equina compression in the dog.

TABLE 4.—*Acute Cauda Equina Compressions (Large Balloons) with Complete Paralysis*

Dog No.	Duration of Compression	Degree of Paralysis at Time of Sacrifice	Interval, in Days, from Compression to Recovery or Sacrifice	Compression Site	Histologic Results
13	6 hr.	100%	39	L3	Moderate rarefaction of spinal cord at compression site and slight thinning of nerve fibers within nerve roots
19	3 hr.	100%	90	L4	Complete cavitation of lower end of spinal cord underlying L5 and extending upward, underlying L4 and L3 laminae; many normal, as well as degenerated, nerve fibers within nerve roots
42	15 min.	0%	26 (Recovery started in 1 day)	L5	Large cavity within posterior columns of lower end of spinal cord underlying L5 lamina. Nerve roots show moderate thinning of nerve fibers. Fat-filled phagocytes are present within spinal cord and nerve roots. Spinal cord is more affected than nerve roots at compression site
43	30 min.	0%	32 (Recovery started in 3-4 days)	L5	Complete destruction of spinal cord at compression site and one segment above it; few nerve roots degenerated but most of them intact; fat-filled phagocytes present within degenerated spinal cord and nerve roots
48	2¼ hr.	0%	45 (Recovery started in 10-20 days)	L5	No histologic abnormality
49	6 hr.	100%	..	L5	Large cavity occupying almost entire spinal cord at compression site and extending upward to T12; cavity filled with monocytes or fat-filled phagocytes; nerve roots normal
60 F	2 hr.	0%	21	L5	Large cavity occupying almost entire spinal cord at compression site; fat-filled phagocytes present within cavity; nerve roots normal
76 F	4 hr.	0%	15	L5	Degeneration of posterior columns at compression site. This area contains many fat-filled phagocytes. Nerve roots show degenerated myelin but axones are normal
54	1 hr.	0%	86 (Recovery started in 4-5 days)	L5	Marked degeneration of conus medullaris and many fat-filled phagocytes present within it; nerve roots of cauda equina normal in Gros-Bielschowsky and Weigert-Pal preparations but axones and myelin sheaths absent in conus and compressed level; some fat-filled phagocytes present in the cauda equina nerve roots which have reduced numbers of nerve fibers
64	3 hr.	0%	75 (Recovery started in 10-20 days)	L5	Marked degeneration of conus medullaris and many fat-filled phagocytes present within it; nerve roots of cauda equina mostly normal in Gros-Bielschowsky and Weigert-Pal preparations but axones and myelin sheaths severely reduced in numbers within conus at compressed level; some fat-filled phagocytes present in those cauda equina nerve roots which show reduced numbers of nerve fibers
73 TA	5 hr.	0%	11 (Recovery started in 2 days)	L5	No histologic abnormality other than some necrosis in gray matter of conus medullaris at compression site; fat-filled phagocytes present in necrotic area

Another difficulty is the variation in the effects of compression at any given level. It has been found, for example, that compression of the dural sac at the sixth lumbar vertebra produces little or no weakness of the hindlimbs. When such weakness is produced, we have found that it results from interruption of function of the nerve roots and not from interruption of the function of the lower end of the spinal cord at this level. But the paralysis produced by compression at the fourth lumbar

vertebral level may be in large part reproduced by severing the spinal cord at this level, as well as by severing the nerve roots. Although severance of the nerve roots underlying the fifth lumbar vertebra results in complete, or almost complete, hindlimb paralysis, a few exceptions to this rule have been found. Also, although severance of the spinal cord at this level usually produces no function change, weakness of the lower limbs occasionally follows.

We have many histologic examples showing that compression effects are more readily transmitted to the spinal cord than the nerve roots (Figs. 6 and 7). Resultant softening or hemorrhage often ascends a segment or two and produces irreversible cord damage at the level of the nerve outflow to the lower limbs. For these reasons we have not been able to carry out a full series of compression tests on the cauda equina. From those cauda equina compressions we have done, however, it is quite clear that, on the basis of functional, histologic, and electrical § evidence, this structure is much more resistant to compression and will tolerate its effect for considerably longer than the spinal cord.

Partial paralysis (20 to 90% complete) occurred in 10 dogs subjected to acute compression of the midthoracic part of the spinal cord. Recovery began one to three days later. This was followed by complete recovery in all dogs. The survival periods varied from 7 to 33 days. There was no histological abnormality of the spinal cords in the animals.

Partial paralysis (10 to 90% complete) occurred in eight dogs with cauda equina compression. Recovery began one to three days later and became complete in all animals. The survival periods were 3 to 15 days. Histologic study revealed no abnormality of the nerve roots, although large cavities were present in the conus medullaris (underlying the fifth lumbar lamina) in two cases. The absence of functional abnormality in these latter animals is due to the fact that the affected area of the spinal cord contained no cells of fibers innervating the hindlimbs. This same type of histologic abnormality occurred in a few dogs which recovered from complete paralysis due to cauda equina compression.

The sequence of motor recovery in all dogs was hips, knees, and, lastly, ankles.

B. Histologic Results.—In those dogs in which complete nonrecoverable paralysis followed spinal cord compression, histologic studies showed extensive destruction of cord, tissue vacuolation, and cavitation at the compression site (Fig. 1), at times extending several segments above and below this site (Fig. 2). Massive hemorrhage of the cord only occasionally occurred (Fig. 3). Hemorrhage and softening of the spinal cord at times coexisted. The cavities were varied in distribution and occupied either or both the gray and the white matter. Large fat-filled or pigment-laden phagocytes and mononucleated cells were seen within and around some of these cavities, in which occasionally there was a little connective tissue meshwork. In one case there was extensive connective tissue scarring in the spinal cord (Fig. 2). In the dogs of this series that recovered there were usually no histologic abnormalities other than occasionally slight cavitation and vacuolization of the white matter at the compression site (Figs. 4 and 5). Occasionally, however, cavitation several times the size of that seen in Fig. 5*A* was present in dogs that had shown complete functional recovery. There was some generalized decreased

§ With the use of the cathode ray oscillograph, the relative susceptibilities of peripheral nerve, nerve roots, and spinal cord to compression are being investigated in our neurophysiology laboratory, under the direction of Dr. S. Gelfan.

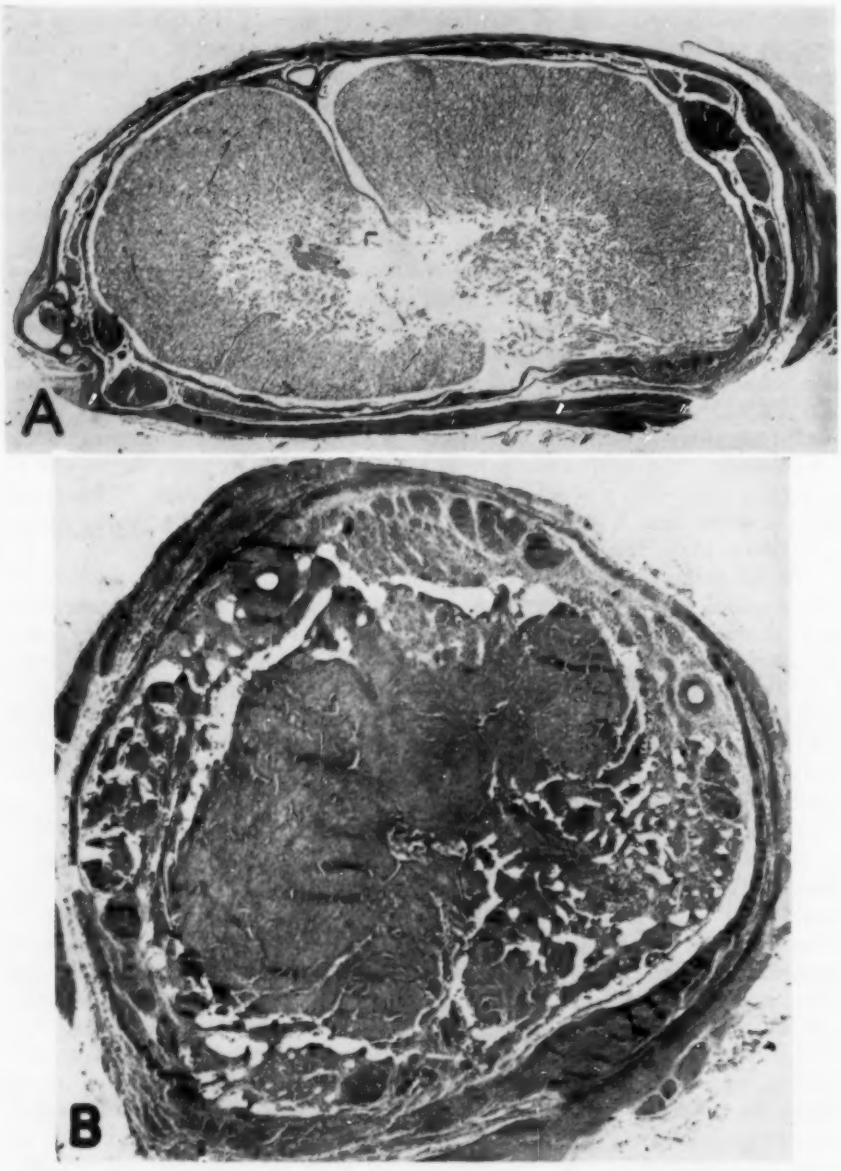

Fig. 1.—Sections through thoracic portion of spinal cord at site of acute compression. *A* was taken from dog subjected to compression for five hours and killed 35 days later. Extensive cavitation is seen. *B* was taken from dog subjected to compression for six hours and killed 150 days later. No functional recovery occurred in these animals.

Hematoxylin and eosin stain; *A*, × 15; *B*, × 16.

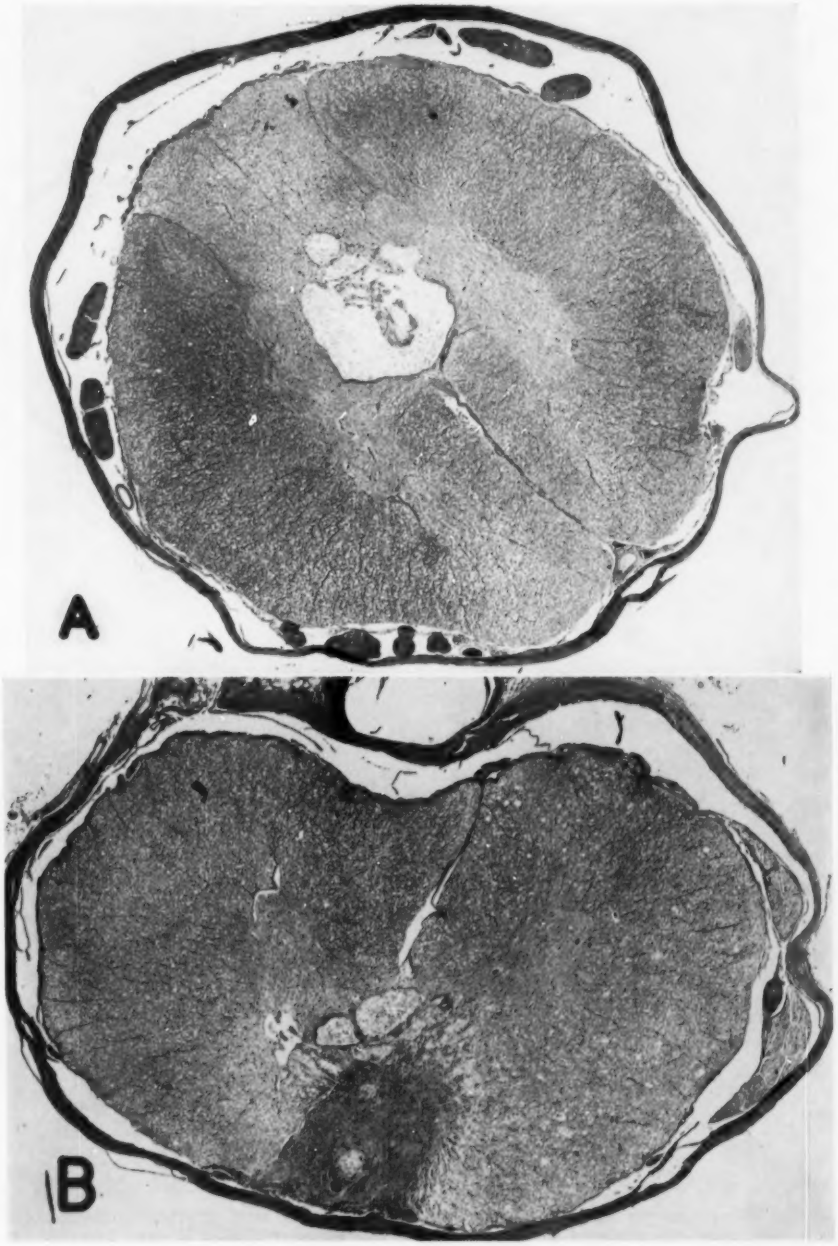

Fig. 2.—Sections taken from fifth and ninth thoracic spinal segments of a dog subjected to compression by a large balloon at the eighth thoracic segment for one and a half hours and killed 10 days later. The sections show the upper and lower limits, respectively, of cord damage. No functional recovery occurred.

Hematoxylin and eosin stains; *A*, × 18; *B*, × 20.

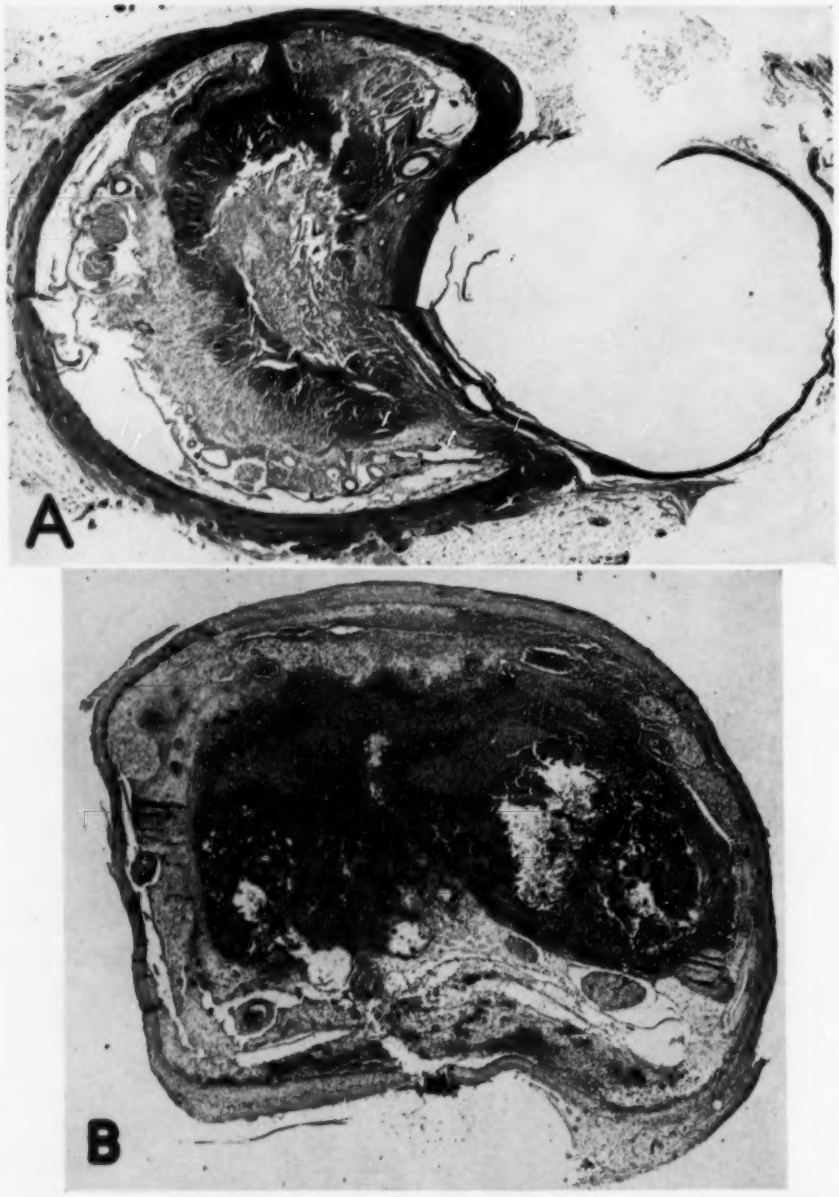

Fig. 3.—Sections through thoracic portion of spinal cord at level of acute compression. *A* was taken from dog subjected to compression for two hours and killed 10 days later. *B* was taken from a dog subjected to compression for one and a half hours and killed 11 days later.

Extensive hemorrhage is seen. *A* shows the softened, hemorrhagic cord compressed by the balloon, the connective tissue capsule of which is shown.

Hematoxylin and eosin stains; × 15.

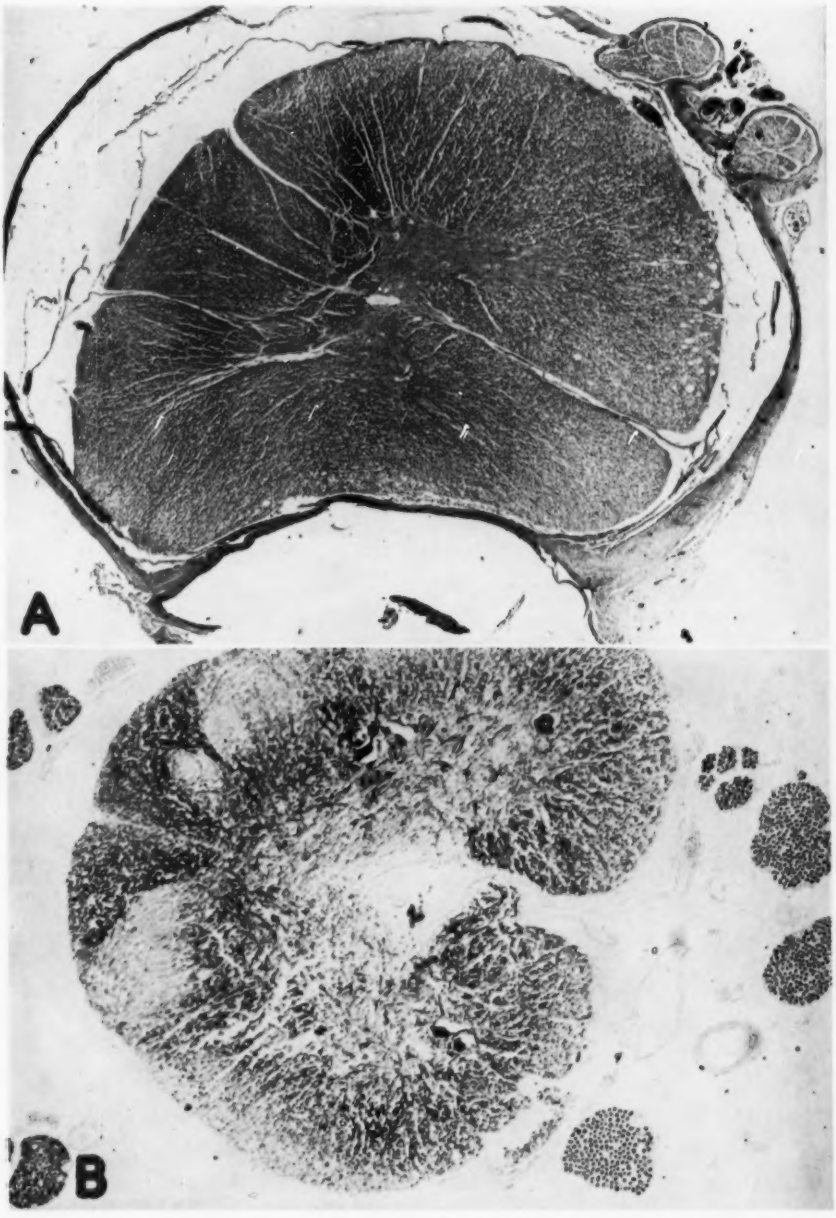

Fig. 4.—*A*, taken from thoracic compression site of a dog that fully recovered from partial paralysis and was killed seven days later. It is of interest that the functional recovery was complete in spite of the distortion of the spinal cord. Hematoxylin and eosin stain; × 16.

B, taken from lower end of conus medullaris in an animal that recovered fully after cauda equina compression (four vertebral segments higher) and complete paralysis of the lower limbs. Gros-Bielschowsky impregnation for axis cylinders; × 50.

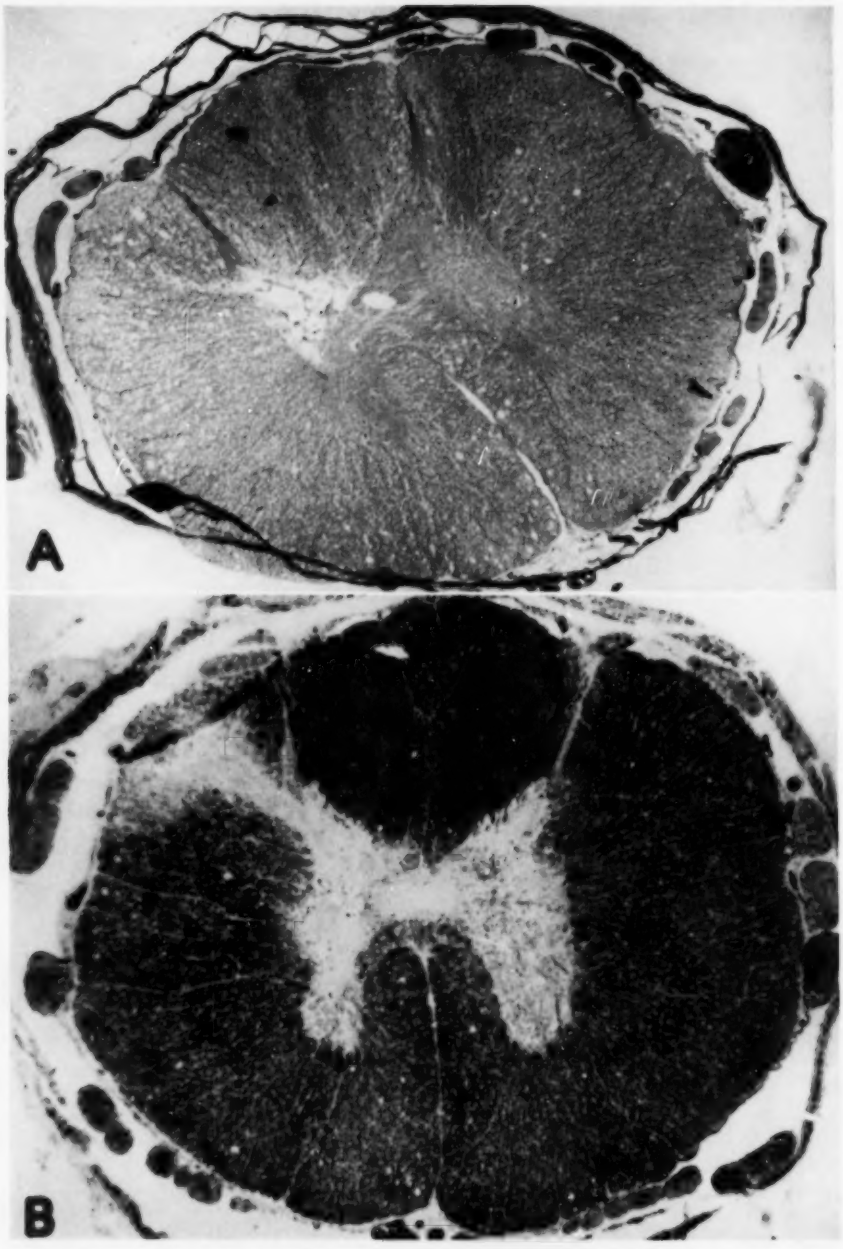

Fig. 5.—Sections taken from thoracic compression site of a dog that fully recovered after a 24-hour period of compression by a medium-sized balloon. Recovery began 3 to 5 days after compression and was complete at the time of sacrifice, 45 days after compression. This animal had pinprick appreciation immediately after compression; otherwise he probably would not have recovered after such a long period of compression. The small area of destruction and demyelination in the posterior gray horn and dorsal root entry zone, respectively, are quite apparent. *A*, hematoxylin and eosin stain, × 19; *B*, Weigert-Pal stain, × 20.

density of nerve fibers at the compression site in some instances. Although counts and measurements of nerve fibers were not done, the loss of nerve fibers did not appear to affect any particular fiber-size group. The site of maximal nerve fiber degeneration was at times ventral and at other times at the compression site, either dorsally or laterally located.

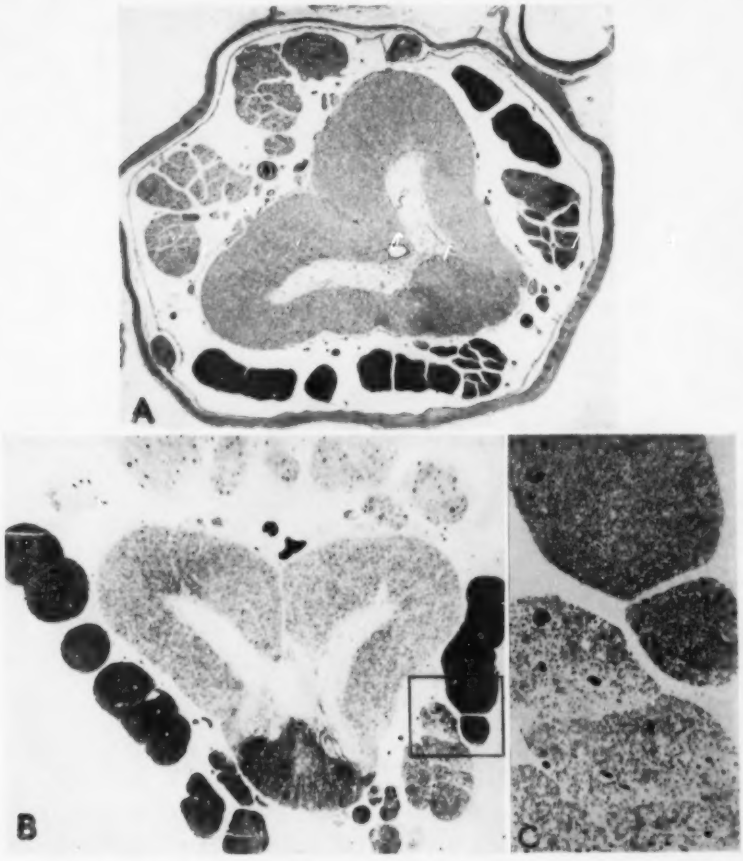

Fig. 6.—Sections through cauda equina at level of fifth lumbar spine. The connective tissue capsule surrounding the compression balloon is seen in *A*. Complete destruction of the gray matter of the conus medullaris is seen, which structure shows also degeneration of the white matter except for the dorsal columns (*B*). The roots ventrally also show myelin degeneration. *C*, taken from the boxed area, shows demyelination of one of the rootlets dorsally. This animal did not recover any function, doubtless because the cavitation extended upward, destroying the lower end of the spinal cord, innervating the lower limbs.

A, hematoxylin and eosin stain; × 11.

B and *C*, Weigert-Pal stains; × 19 and × 55, respectively.

We had the opportunity of examining many spinal cords in dogs that died within a week or two after compression. Data on these animals were not included in the Tables because their survival periods were not sufficiently long to enable one to draw

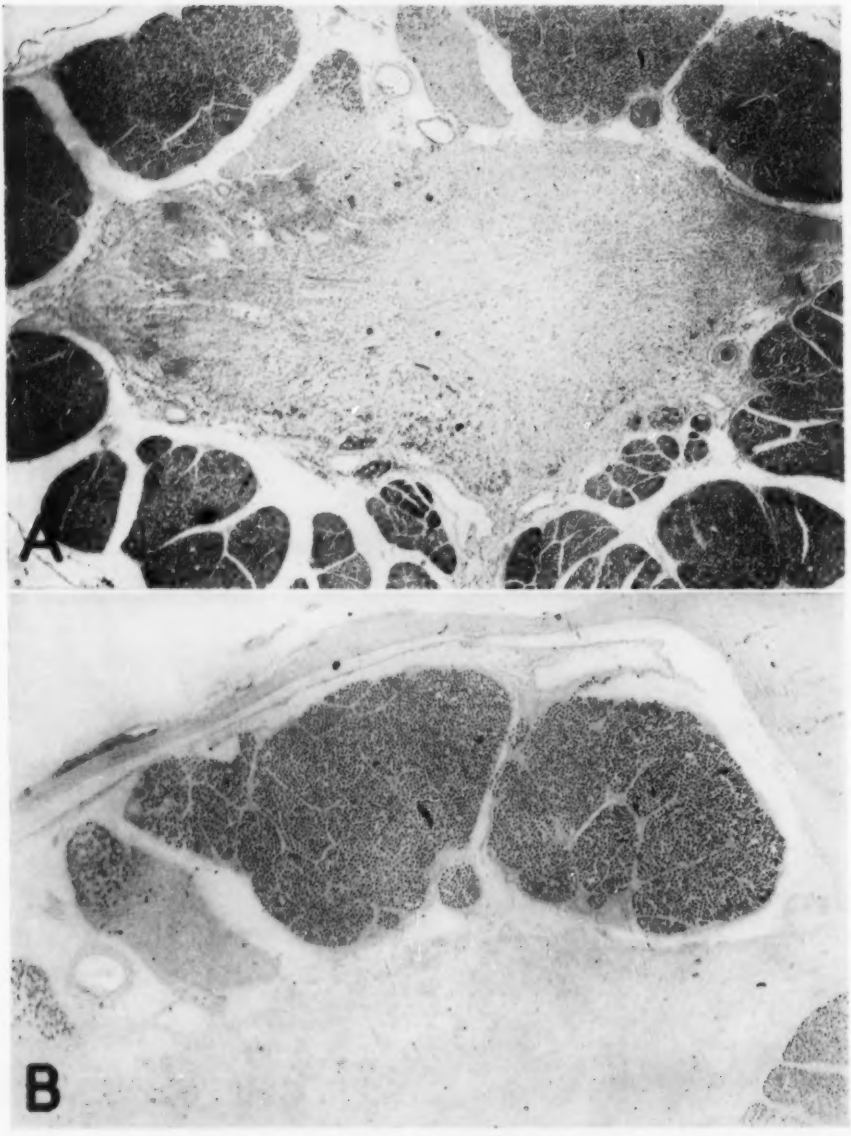

Fig. 7.—Sections taken from cauda equina at the sixth lumbar vertebral level. The dog was subjected to compression at this level for 30 minutes. Total paralysis followed. Recovery began three to four days later and was complete 32 days after compression. There is marked destruction of the conus medullaris, but the axones of the cauda equina nerve roots are normal. Gros-Bielschowsky impregnation for axones, *A*, × 7.5; *B*, × 40.

deductions concerning the recoverability of function. However, histologic preparations of those spinal cords show considerable vacuolation, indicating edema at this stage. Normal ganglion cells, at times coexistent with chromatolytic ones, were present near areas of spinal cavitation at the compression site. There was no indication of a greater effect on ganglion cells than on any other neural structure at any time after compression. In some animals there was more destruction of myelin sheaths than of nerve fibers at the compression site, but these differences were neither constant nor very striking.

In dogs in which complete nonrecoverable paralysis followed cauda equina compression, histologic studies revealed massive cavitation of the conus medullaris or, in a few cases, massive hemorrhage into it. This destructive change occurred at the compression site and at times extended upward for a segment or two. Some of the surrounding nerve roots showed degeneration (Fig. 6). Connective tissue scarring of the roots, only occasionally present, was slight. There was much greater destruction of the spinal cord than of nerve roots at the compression site (Fig. 7). Fat-filled phagocytes within the nerve roots and spinal cord were present at the sites of the compression as long as three months after the operation.

It was not possible to demonstrate selective destruction of any particular spinal pathways by the compression, although occasionally the nerve fibers seemed to have been somewhat more damaged immediately adjacent to the balloon than elsewhere. In cases of complete destruction of the thoracic spinal cord at the compression site, Weigert-Pal and Gros-Bielschowsky preparations taken from the upper thoracic region showed marked degeneration of the posterior columns and some thinning anterolaterally. The lower thoracic and upper lumbar levels of the spinal cord showed moderate degeneration of the posterolateral and, to a less extent, of the anterolateral columns. Large parts of the anterior and lateral, and somewhat less of the posterior, columns showed no degeneration. This was true also after sharp transection of the midthoracic spinal cord.

The site of the rubber balloon was indicated by a connective tissue capsule that had surrounded the balloon and was adherent to the dura mater. Study of control animals showed that this connective tissue encapsulation of the balloon caused no changes in the spinal cord.

COMMENT

The effects of compression producing complete sensorimotor paralysis are essentially those of a complete physiologic transection. The inflated balloon tends to occupy the entire available space within approximately a centimeter or less of the vertebral canal. Roentgenograms reveal that under these conditions the spinal cord must be flattened into a thin ribbon between the balloon and the bony surface of the vertebral canal. Functional recovery from such acute compressions proves that the transection was not anatomical or irreversible when the duration of compression was relatively short (one minute for large compressive forces, 30 and 120 minutes for medium and small forces, respectively).

In evaluation of the respective roles of mechanical and ischemic factors in causing paralysis due to compression, the time of onset of paralysis and recovery from it are of decisive importance.

The onset was instantaneous in all cases of acute total sensorimotor paralysis. Recovery from spinal cord compression of large magnitude applied for only one minute did not begin until a day or two afterward. In the dog whose spinal cord

was compressed with a large balloon for five minutes, recovery did not begin until 10 to 18 days afterward. The instantaneous onset of paralysis with great compression and the delayed onset of recovery from it exclude ischemia as a significant causal factor for the following two reasons: First, it has been demonstrated that there is a minimal latent period of from one to four minutes before even the most vulnerable spinal cord structures cease functioning after complete anoxia, asphyxia, or ischemia of the spinal cord.‖ Second, recovery from as long as a five-minute bout of total ischemia begins in a few minutes.[4] Furthermore, whereas there was no recovery from a two- or three-minute period of compression in two dogs and none from periods of over five minutes of compression in any dogs in our large-balloon series, recovery always occurs after bouts of total ischemia of the lumbosacral spinal cord for as long as 25 minutes.[5] We must therefore conclude that with large compressive forces the functional loss resulted from mechanical deformation of the spinal cord rather than from ischemia.

The compressive forces of our balloons, which simulate to some degree those produced by expanding extradural tumors, are obviously not exerted equally upon all spinal cord components. The placement of such a balloon must necessarily be eccentric. Some degree of displacement of the spinal cord or its nerve roots, or both structures, seems possible before conduction block or other injury occurs. However, because of the deep location of the anterior spinal artery and the presence of the several radicular arteries at a given segment, it is unlikely that a compressive force could occlude the arterial circulation sufficiently to produce complete localized ischemia without seriously deforming the spinal cord. The anoxia in such a case could hardly be total.

It might be argued that even a partial ischemia sufficiently prolonged would produce an anoxic block and eventually, if the ischemia is unrelieved, irreversible damage. However, even with minimal compressive forces producing complete sensorimotor paralysis, the immediate onset of the paralysis and the delayed recovery from it, while not excluding localized ischemia entirely as a factor causing the paralysis, nevertheless point unmistakably to mechanical deformation as more decisive in producing the effects observed with the smaller-balloon compressions.

The minimal latent period for the beginning of recovery from complete paralysis produced by the small balloons was nine days. All of Tureen's cats could walk within 24 hours after operation (ether anesthesia), during which the thoracic aorta was clamped below the arch.[13] Motor power returned in most of his animals in from three to five hours. Krogh's somewhat similar experiments on rabbits more or less confirm these findings.[8] The longest latent interval for the return of all tested muscle reflexes after 25 minutes of complete asphyxia of the lumbosacral cord of spinal cats as produced by van Harreveld and Marmont was nine hours.[5] Our one dog whose spinal cord was successfully compressed with a small balloon for only 15 minutes did not begin to recover from the paralysis until 16 days after decompression.

All of our dogs whose spinal cords were compressed for 15 to 120 minutes with small balloons recovered completely and showed either no or relatively slight histologic abnormality. Histologic studies by van Harreveld of cats asphyxiated for 55 minutes showed only an occasional normal cell in the gray matter of the spinal cord.

‖ References 4, 6, 7, and 9.

The histologic changes in the spinal cords of our dogs consisted of vacuolation, deformation, and disruption of tissue and hemorrhage. Some chromatolysis of ganglion cells occurred, but there was no predilection of any histologic abnormality, except possibly hemorrhage, for the gray matter. Because anoxia affects primarily ganglion cells, one may conclude that our histologic changes were chiefly the result of some other factor.

These facts emphasize the mechanical as the main factor in paralysis due to spinal compression. One may also conclude from them that the chances of recovery from the effects of compressions maintained by forces of small magnitude for as long as two hours are very much better than from the effects of total ischemia maintained for comparable periods.

When compression produced complete paralysis but spared pain sensation, the spinal cord withstood the compression for as long as one to three weeks. Almost complete or considerable functional recovery followed its release in these dogs.

Complete recovery from totally lost sensory and motor function below the compression site occurred after cauda equina compression for as long as five hours. The failure of function to return to the hindlimbs after cauda equina compression for shorter periods in some dogs at first surprised us. Our histologic studies show that the explanation lies in the ascent of cavitation and hemorrhage in the conus medullaris to that part of the spinal cord innervating the hindlimbs. We have seen many histologic examples of the greater vulnerability of the spinal cord than of nerve roots to compression.

Severe scarring of the nerve roots of the cauda equina did not occur in any case. Regeneration of the posterior nerve roots would, of course, not ensue, but, in the absence of impenetrable scarring, regeneration of the anterior roots would occur. The absence of motor recovery in these cases is attributable to the spinal cord rather than to the nerve-root damage. Although chromatolytic changes occur in the motor cells of an interrupted nerve, the changes are reversible, and the power of outgrowth of nerve fibers persists for a very long time—in fact, as long as 3,164 days after injury in a human case reported by Bowden and Gutmann.[3] Functional recovery, however, was impossible in this case because of the extreme muscle atrophy. In the absence of severe scarring of nerve roots, which does not seem to occur readily, and in the absence of severe muscle fibrosis, recovery would be expected to occur even after long periods of compression of the cauda equina.

Our experiments show clearly that the pain fibers in the spinal cord, and also in the cauda equina, are much more resistant to compression than motor and position sense fibers and that they usually recover before the latter after the compression is released.

SUMMARY AND CONCLUSIONS

Functional recovery after acute extradural compression of the spinal cord in dogs depends upon the magnitude of the compressive force, as well as on its duration.

With large compressive forces, full recovery of function occurred when the compression was released in one minute. When such compression was applied for longer periods, functional recovery did not usually occur. The cause of these irreversible changes is destruction of the spinal cord at the compression site.

When minimal spinal compressive force is used to produce paralysis of the hindlimbs and complete sensory loss, recovery occurs with periods of compression

up to two hours. When a compressive force of intermediate grade is used, the critical period is 30 minutes, beyond which there is no return of function.

Compression of the cauda equina by large balloons for as long as five hours is compatible with full functional recovery after its release. Failure of recovery to occur within this period, and probably after longer periods of compression, is due to hemorrhage within the conus medullaris, which diffuses upward to destroy the adjacent segment or two of the spinal cord innervating the hindlimbs.

Although functional recovery may begin as early as 1 to 5 days after spinal cord or cauda equina compression, it may be delayed as long as 30 days after spinal cord compression and 59 days after cauda equina compression in dogs in which full return of function follows.

A comparison of the effects of ischemia with those of spinal compression in our animals shows that mechanical deformation, rather than anoxia, is the main factor in producing compression paralysis.

Pain sensation persists after motor function of the hindlimbs is lost after compression of the spinal cord and cauda equina, and during the recovery phase it returns before motor power and position sense.

The duration of spinal cord compression compatible with recovery is much longer in animals—up to one week and more—which show complete loss of motor function but preserved pain sensation.

The less the degree of sensorimotor paralysis after acute compression, the more quickly does recovery ensue.

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STURGE-WEBER-DIMITRI SYNDROME

Cephalic Form of Neurocutaneous Hemangiomatosis

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THE ANATOMICAL basis for Sturge-Weber-Dimitri syndrome is a hemangiomatous dysplasia in the cephalic region. Since port-wine nevi are frequently found also on the trunk and extremities, the syndrome may be considered as a partial or regional manifestation of generalized neurocutaneous hemangiomatosis. As such, it may be classified along with von Recklinghausen's disease, tuberous sclerosis, and neurocutaneous melanomatosis, for in all of these disorders the skin manifestations indicate the possible presence of changes in the nervous system, as well as in other systems. The clinical features of the syndrome are a vascular nevus of the face, associated with signs of cerebral dysfunction, such as epilepsy, mental deficiency, and hemiplegia, and roentgenographic evidence of sinuous shadows within the cranial cavity. The skin lesion is generally a nevus flammeus of the face or scalp, which often exhibits striking evidence of being confined to the areas of distribution of branches of the trigeminal nerve. The lesion is usually unilateral but may be diffuse over both sides of the face, in which case the neural changes are often limited to the side more severely affected. The vascular anomaly may also involve the conjunctiva and the choroid layer of the eye, and associated lesions may occur in the mouth, nose, and throat. As in the other neurocutaneous syndromes, incomplete or central forms are recognized in which there are no visible superficial lesions. Commoner, however, are the incomplete cutaneous forms in which a nevus flammeus of the face is unassociated with clinical or roentgenographic evidence of brain disease.

The nomenclature of this syndrome has varied considerably from descriptive terms, such as encephalotrigeminal angiomatosis, to eponyms, such as Sturge-Weber disease, Sturge-Weber-Dimitri disease, Krabbe's disease, Parkes Weber-Dimitri disease, Weber-Dimitri disease, and Sturge-Kalischer disease. The first reports have been ascribed to Sturge [1] (1879) and Kalischer,[2] Volland [3] (1913) described the case of a feebleminded and epileptic boy who had a vascular nevus on the left side of his face and a contralateral hemiplegia. Autopsy revealed atrophy of the left cerebral hemisphere, hemangiomatosis of the overlying leptomeninx, and sclerosis of the underlying cerebral cortex. Weber [4] (1922) and Dimitri [5] (1923) described

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the characteristic roentgenographic changes, while Krabbe[6] (1934) described the granules of lime salts in the second and third layers of the cerebral cortex which produced the sinuous x-ray shadows.

The present study consists of one clinical and two clinical-pathological reports of Sturge-Weber-Dimitri syndrome.

REPORT OF CASES

CASE 1.—*History.*—J. R., a white man, was born on Nov. 25, 1904. He was first in order of birth and full term. The labor was reported to have been difficult, and it is said that he weighed only 3.5 lb. (1,588 gm.) at the age of 5 months. Convulsions were first noticed at 9 months of age, and shortly thereafter his parents recognized that he did not use his right upper extremity as well as the left. He was admitted to the Lincoln State School and Colony on July 19, 1910, where he remained until Sept. 4, 1922, when he was transferred to the Dixon State Hospital.

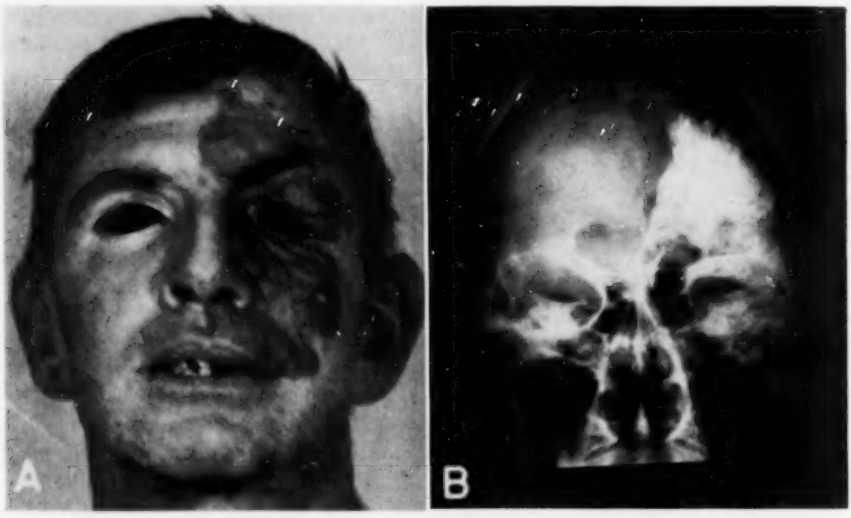

Fig. 1 (Case 1).—Photographs, showing the nevus flammeus of the face, in *A*, and the calcified atrophic cerebral cortex, in *B*.

Clinical examination revealed a well-nourished man with a hemangioma over the left side of the face (Fig. 1*A*). It extended to the midline over the forehead, bridge of the nose, and upper lip, while its lateral margin was somewhat irregular and on a vertical line parallel to the outer margin of the eye. There was a very marked right spastic hemiplegia; the elbow, wrist, and phalangeal joints were flexed, while the lower extremity was extended. The right upper and lower extremities were smaller than those on the left side. The pupils were round and equal and reacted both to light and on convergence. Records showed that the patient had repeated convulsions, which at times were as many as 10 in one month. An electroencephalogram revealed an abnormally slow record with amplitude asymmetry, the amplitude being lower on the left side. Roentgenograms of the skull revealed a large area of increased density involving the entire left cerebral hemisphere. In an anteroposterior view (Fig. 1*B*), the shrinkage of the hemisphere was evidenced by the increased distance between the convexity of the brain and the inner table of the skull. The midsagittal plane was deviated toward the left, the deviation being greater as the convexity was reached. Lateral and axial views of the skull showed the characteristic double contour lines, which resembled calcified sinuous blood vessels (Fig. 2). In some views, however, it was evident that the linear densities outlined the cerebral convolutions.

Comment.—The cutaneous, neurological, and roentgenographic findings are those of a classical example of Sturge-Weber-Dimitri syndrome. The details of the histopathological changes found in the brain in such instances will be described in the succeeding clinical-pathological studies.

CASE 2.—*History.*—V. M., a 19-year-old woman, was admitted to the Dixon State Hospital in December, 1950. It was impossible to obtain a detailed history of the case, but it was reported that she was apparently well until the age of 4 years, when she had a grave illness, diagnosed as encephalitis, after which her physical and mental development was retarded. She was extremely small for her age, weighing only 46 lb. (20.9 kg.). Her chest was deformed; there was a marked kyphoscoliosis, and all four extremities were paralyzed. There were tonic and clonic seizures and a few athetotic movements. Many of her deep reflexes could not be obtained because of the extreme spasticity. Her speech consisted of a few grunting sounds, and the intelligence was extremely low. The pupils reacted to light and on convergence, and the optic fundi were normal. The skin was the seat of a dry eczema, but no hemangioma was evident. The urine examinations were negative for phenylpyruvic acid. Death resulted from aspiration bronchopneumonia.

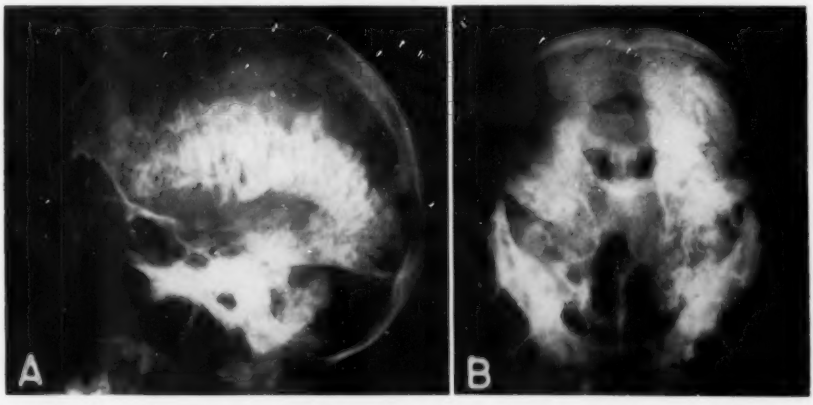

Fig. 2 (Case 1).—*A*, lateral and, *B*, axial views of the skull, showing the characteristic double-contour radiopaque linear shadows.

Gross Pathological Observations.—The formalin-fixed brain weighed 923 gm. The right cerebral hemisphere was smaller than the left, and its leptomeninges were the seat of an increased number of thin-walled veins. Roentgenograms of the brain revealed double-contour, tortuous, sinuous shadows in the occipital (Fig. 3*A*) and frontal regions. On cutting the brain into coronal segments, the knife encountered gritty material, and these granulations could be seen grossly within the cerebral cortex. The entire pallium on the right side was atrophic as compared with the left.

Microscopic Observations.—Sections were taken for microscopic study from representative areas of the brain. In a preparation of a coronal section from the right frontal lobe, stained according to Weil's method and counterstained by the Van Gieson method, the characteristic pathologic alterations were demonstrated. The leptomeninges were of normal thickness, but at many sites the subarachnoid spaces contained innumerable thin-walled veins engorged with blood (Fig. 3*B*). The pallium covered by this excessive vascularization showed a variety of pathologic alterations, which varied in intensity from place to place (Fig. 3*C*). The capillaries within the cerebral cortex were covered with concretions in the form of beads, which in places coalesced to form pericapillary sheaths (Fig. 4*A*). In some fields the adventitia of the capillaries and precapillaries was thickened and stained deep red. Many of the capillaries and venules in

both the cortex and the subcortex were engorged with blood. In regions where the pathological alterations were much more advanced, one saw innumerable spherical, laminated concretions which had coalesced to form mulberry-shaped masses (Fig. 4*B*). In places, the subcortical white substance was the seat of thick-walled veins, and the surrounding areas were degenerated, gliotic, and the seat of innumerable concretions that varied in size and shape (Fig. 4*C*). In some fields, dilated spiral-shaped veins could be followed from the subarachnoid space down through the cerebral cortex into the medullary substance. In thionine preparations, one could follow the neuronal and neuroglial reaction. Where the changes were very marked, there was complete disorganization of the ganglionic layers and a great deficit in nerve cells. Many of the remaining

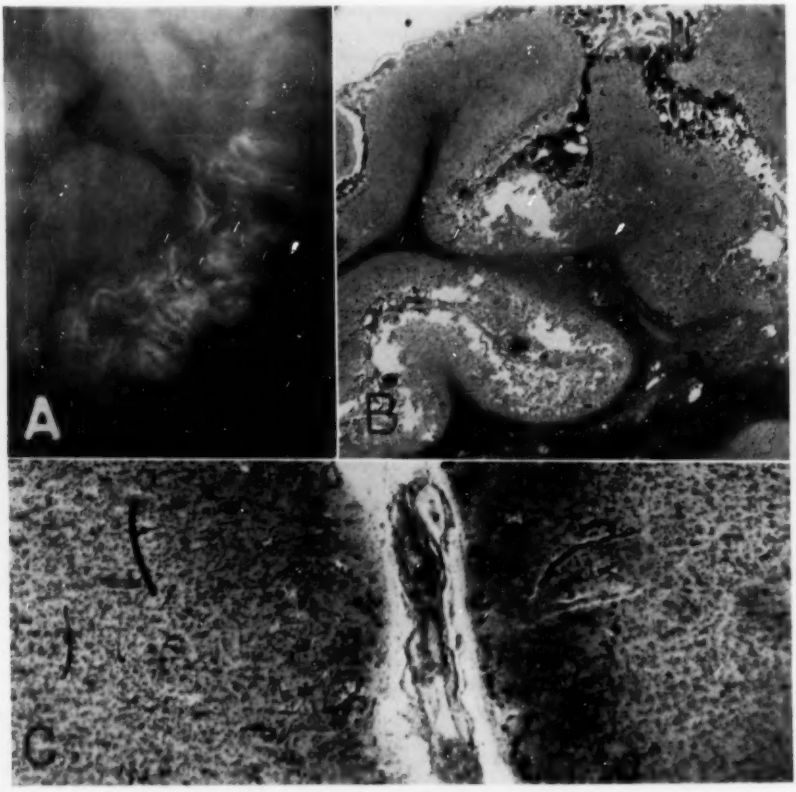

Fig. 3 (Case 2).—*A*, roentgenogram of the occipital pole of the formalin-fixed brain, showing the characteristic linear shadows. *B*, low-power photomicrograph, showing the excessive vascularization of the leptomeninx and the disorganization of the cerebral cortex; Weil-Van Gieson stain. *C*, higher-power photomicrograph of two neighboring convolutions, showing the intracortical calcifications; Nissl stain.

nerve cells were shrunken and devoid of Nissl substance. In some fields one could see a diffuse deficit in nerve cells without either calcification or gliosis, and in other fields the gliosis was intense and the calcification very limited in extent or not present at all. The choroid plexus in the temporal horn of the left lateral ventricle was the seat of a hemangiomatous malformation, its greater portion being composed of dilated veins, engorged with blood. Attempts to demonstrate iron by histochemical means were unsuccessful, but preparations for the demonstration of calcium showed the calcifications to be composed of this substance.

Comment.—The absence of signs of a vascular nevus of the face, scalp, nose, or throat; the presence of an excessive number of veins in the leptomeninx covering the right cerebral hemisphere, and the roentgenographic evidence of linear radiopaque shadows outlining the cerebral convolutions permit one to consider the case as an incomplete form of Sturge-Weber-Dimitri syndrome. Histologically, the major alterations in the cerebral cortex represented changes that were interpreted as being secondary to the hemangiomatosis of the overlying leptomeninx. The subcortical medullary substance, however, had primary areas of degeneration and calcification associated with localized foci of hemangiomatosis, as well as areas of secondary degeneration.

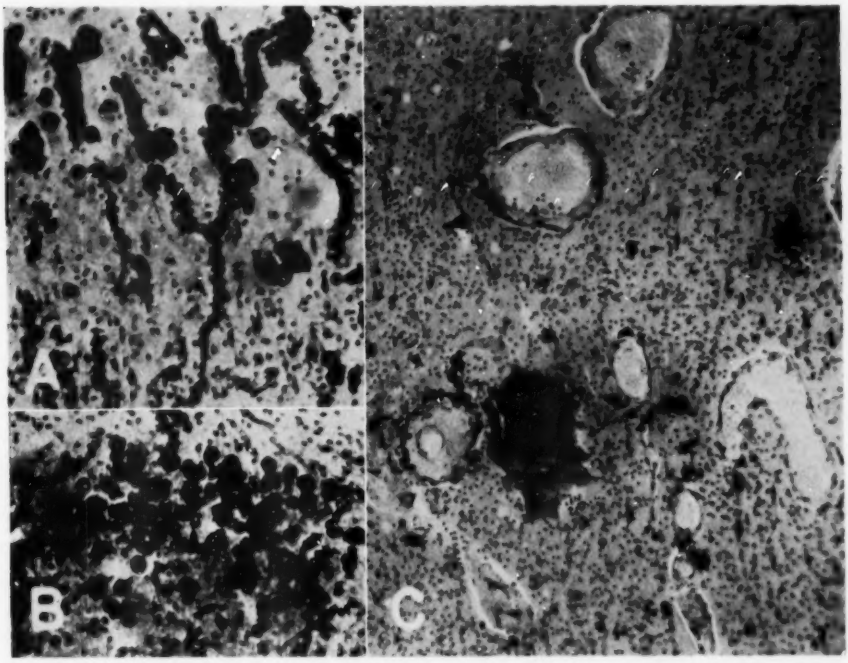

Fig. 4 (Case 2).—Higher-power photomicrographs, showing, in *A*, the pericapillary beading and sheathing; in *B*, the compact, dense concretions in the subpial zone, and, in *C*, the anomalous veins, concretions, and gliosis in the subcortical medullary substance; Nissl stain.

Case 3.—*History.*—D. M., a 21-year-old man, was admitted to the Dixon State Hospital as a voluntary patient on three occasions. Seizures began between the ages of 1 and 2 years, and these recurred at frequent intervals. He had all of the common childhood diseases, but the exact date of onset of his right hemiparesis could not be determined. The convulsions and hemiparesis were attributed to encephalitis. He was frequently subject to attacks of status epilepticus, and, after having 11 major seizures within two hours in August, 1951, he remained in a prolonged state of semiconsciousness. Between his second and third admissions to the hospital, his mental status deteriorated markedly. The major physical findings were a hemangioma on his forehead and spastic hemiplegia with underdevelopment and atrophy of the right upper and lower extremities. Death occurred on Sept. 7, 1951, after an acute attack characterized by cyanosis, rapid respirations, and elevated temperature.

Gross Pathological Findings.—Aspiration bronchopneumonia, venous angioma of the leptomeninges over the convexity of the left cerebral hemisphere in the central and paracentral regions, and convolutional atrophy of the brain beneath the leptomeningeal hemangioma.

Brain: The formalin-fixed brain weighed 1,351 gm. The superior surface of the convexity of the left cerebral hemisphere was the seat of an increased number of large, tortuous veins. This area extended 5 cm. anteroposteriorly and bordered medially on the sagittal fissure. Its greatest width was in the central region, where it measured up to 5 cm. Coronal sections of the brain

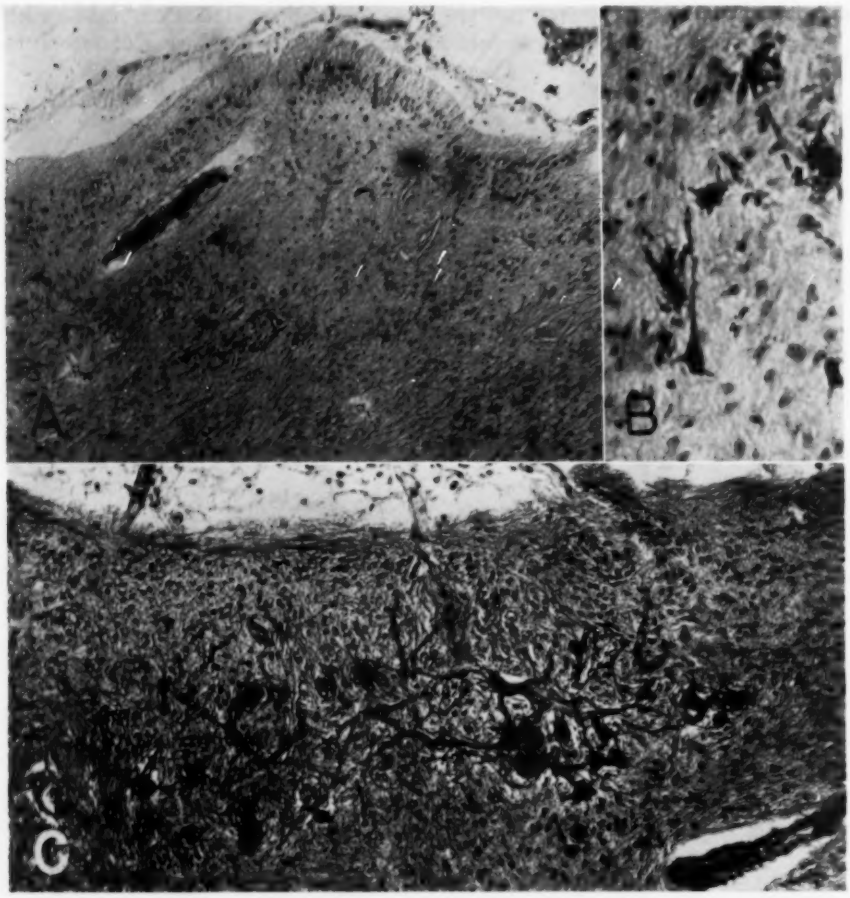

Fig. 5 (Case 3).—*A*, low-power photomicrograph, showing the sclerotic atrophy of the cerebral cortex; *B*, higher-power photomicrograph, showing the calcified nerve cells; Nissl stain. *C*, low-power photomicrograph of the cerebral cortex, showing the perivascular fibrosis and obliteration of the capillary bed; Weil-Van Gieson stain.

revealed convolutional atrophy of the gyri beneath the dilated veins. The midportion of the left lateral ventricle was much larger than the right, and the corpus callosum was atrophic in the affected area. X-rays of the formalin-fixed brain revealed double contour lines of increased density, which outlined the atrophic gyri.

Microscopic Observations.—Blocks of tissue were taken from representative areas of the brain, and sections were prepared according to a variety of staining methods and impregnation

techniques. The major pathological alterations were restricted to the areas that appeared grossly abnormal. In these regions, the subarachnoid spaces were the seat of large numbers of medium-sized veins engorged with blood, and the leptomeninges were hyperplastic. Two types of pathological changes were observed in the cerebral cortex. In some gyri, many of the capillaries of the normal vascular bed were surrounded by beads of amorphous material, which in places coalesced to form pericapillary sheaths. The cytoarchitecture in the vicinity of these alterations was disorganized; many of the nerve cells were atrophic, and there was an increase in the number of astrocytes and microglia. In other convolutions, the alterations were entirely different. Here one observed changes which may be designated as sclerotic atrophy of the cerebral cortex (Fig. 5). There was a complete absence of nerve cells with a very dense overgrowth of fibrillary glia. The pia-glial membrane was hyperplastic, and the nuclei of the astrocytes in the subpial zone of the cortex stood out prominently. The middle zone of the sclerotic cerebral cortical convolutions was the seat of a branching network of obliterated blood vessels, whose adventitia was hyperplastic, staining bright red with Van Gieson's method. Scattered throughout the sclerotic areas were single, spherical concretions and a considerable number of incrusted nerve cells. The medullary substance beneath the atrophic convolutions was degenerated and appeared pale in Weil preparations.

Comment.—This case presented the complete form of Sturge-Weber-Dimitri syndrome, namely, facial and leptomeningeal hemangiomatosis, linear radiopaque shadows in roentgenograms of the brain, and hemiplegia, epilepsy, and mental deficiency. The areas of sclerotic atrophy of the cerebral cortex represented regressive changes secondary to the leptomeningeal hemangiomatosis, but the complete loss of nerve cells early in life possibly resulted in a failure in blood flow to the affected areas, and hence no calcification.

GENERAL COMMENT

From the clinical and pathological data presented, it is evident that we are dealing with the basic features of the Sturge-Weber-Dimitri syndrome. The *sine qua non* of this syndrome is the hemangiomatosis, which is generally limited to the mesenchyma lying in proximity to the ectoderm. As such, the vascular nevi are found in the skin, the conjunctiva, the choroid layer of the eye, and the leptomeninx. An identical distribution has been noted in instances of neurocutaneous melanomatosis, although the changes have not been so widespread in the cephalic region. The experimental work of Harvey and Burr [7] has shown that the neural crest gives rise to a variety of histoid elements, among which are the nerve cells of the cerebrospinal ganglia, their capsule cells, and the mesenchyma which goes to form the leptomeninx. DuShane [8] has presented experimental evidence that the cutaneous pigment cells arise from the neural crest. The sharp limitation of the cutaneous vascular nevus to the areas of distribution of branches of the trigeminal nerve suggests that the dysplastic vascular mesenchyma may have migrated from the region of the neural crest along with the developing nerves and that the same dysplastic tissue produced the hemangiomatosis of the leptomeninx. The frequent association of pigmented nevi of the skin with vascular nevi serves to emphasize their probable relation to their anlage—the neural crest.

Hemangiomatosis may affect single organs, the skin, the brain, the kidney, etc., or it may be limited to segments or regions of the body. Cutaneous hemangiomas of the skin over the spinal region have been associated in some instances with hemangiomas of the underlying vertebra, the spinal leptomeninges, and the spinal cord itself. The unusual feature of Sturge-Weber-Dimitri syndrome is the secondary

changes in the brain and not the primary hemangiomatous dysplasia. There are a variety of hemangiomatous states, and not all of them result in calcification of the cerebral cortex. Angiomas and telangiectases occur in Osler's disease (hereditary hemorrhagic telangiectasia), the lesions having been described in the skin, meninges, and brain.

An analysis of the pathological alterations in Sturge-Weber-Dimitri syndrome reveals the following features: an excessive number of thin-walled veins in the leptomeninx; an excessive number of blood vessels, chiefly veins and precapillaries, in the subcortical medullary substance; pericapillary sclerosis in the cerebral cortex underlying the excessively vascularized leptomeninx, with extreme disorganization of the cytoarchitecture and gliosis; sclerotic atrophy of the cerebral cortex with complete loss of nerve cells, extensive gliosis and pericapillary fibrosis, and sclerosis and degeneration of the subcortical medullary substance.

The veins in the leptomeninx appeared perfectly normal but increased in number. The term venous hemangiomatosis probably describes this state most accurately. The group term hamartomatosis may be used to designate this state, in which there is a tumor-like mass composed of tissue normally present in an organ or structure. Some dilated veins could be followed through the cerebral cortex into the medullary substance, but the morphological alterations in the cerebral cortex *per se* appeared to be entirely secondary phenomena. In the medullary substance, some of the veins showed marked fibrosis, whereas in others the wall was entirely calcified.

Close inspection of the roentgenograms of the brain reveals that the double-contour linear densities outline not blood vessels but, rather, the cerebral convolutions. The changes could be followed from pericapillary beading to coalescence of the beads to form sheaths, which in places became very dense, forming spherical and mulberry-shaped masses. The changes were not limited to any particular layers of the cerebral cortex, and, in some fields, its entire width was replaced by irregular masses. When capillaries were followed from the pia-mater into the cerebral cortex, the sharp delineation of the concretions to the brain substance was evident, the veins and capillaries of the pia being unaffected. In other fields, the cerebral cortex underlying the venous hemangiomatosis of the leptomeninx was strikingly devoid of pericapillary concretions. In these cortical areas, there was a complete absence of nerve cells, an intense gliosis, and pericapillary fibrosis of the obliterated vascular bed. Scattered throughout were calcified or incrusted nerve cells and an occasional calcified capillary. The histopathological alterations were those commonly observed in instances of infantile cerebral paralysis resulting from anoxia.

The nature of the sclerotic substance in the cerebral cortex which appears as radiopaque densities has been studied extensively. Although the majority of the densities can be identified as calcifications histochemically, in one reported by Lichtenstein and Rosenberg [9] the pericapillary sclerosis, as well as the nerve cell incrustations, gave a positive reaction for iron. In the two cases reported in the present study, some of the masses gave a positive reaction for calcium, while other masses were negative for both calcium and iron. The histodynamics of calcification and ferrugination have not been decided with certainty, but it appears that certain metabolic disturbances in the brain are associated with the deposition of a colloidal substance, which then becomes the nidus for the deposition of calcium and iron salts. In a recent study by Wachsmuth and Löwenthal,[10] a careful analysis was

made of the mineral elements in the intracerebral calcifications of Sturge-Weber-Dimitri syndrome. Such analyses must be performed on unfixed tissue, for fixation, washing, and staining play a role in altering the constituents.

There is no consensus on the dynamics of the cerebral cortical changes. My observations are in accord with those of Bergstrand, Olivecrona, and Tönnis,[11] who attribute the densities to sclerosis of capillary blood vessels. Even in the larger mulberry-shaped concretions one can find central cores, which represent capillaries. Of greater interest are the areas of cortical sclerosis more or less devoid of calcification. These areas have been ascribed to primary aplasia or maldevelopment with secondary gliosis. The work of Alexander and Woodhall [12] on calcification of the brain resulting from incomplete interference with the circulation casts light on the probable dynamics of the cerebral cortical changes in Sturge-Weber-Dimitri syndrome. The venous hemangiomatosis of the leptomeninx results in capillary stasis and lowered metabolic activity. The deposition of calcium and/or iron tends to increase the hematoencephalic barrier, leading to greater interference with the nutrition and more profound metabolic changes. It is for this reason that the calcifications and the clinical picture progress, while there is no evidence that the hemangiomatosis is an active proliferative process. The areas of the cerebral cortex that exhibited complete loss of nerve cells, intense gliosis, and pericapillary fibrosis of the vascular tree probably represent the effects of anoxia brought on by venous stasis very early in life, that is, in infancy or in the latter months of gestation. With the complete disappearance of nerve cells and the establishment of the reactive gliosis, the circulation is reduced to such a minimum that calcification does not occur.

In a sense, there is nothing pathognomonic about the calcification of the cerebral cortex in Sturge-Weber-Dimitri syndrome, for other pathological states interfering with the metabolism, but not with the arterial blood supply, produce a similar picture. In a study of a meningotheliomatous meningioma by Lichtenstein and Lev,[13] calcifications were noted in the underlying cerebral cortex, and, in the report of a pial lipoma by Scherer,[14] the cerebral cortex beneath the lipoma presented both types of changes reported in this study, namely, gliosis and deficit in nerve cells, as well as pericapillary sheathing. Cerebral calcification occurs in a variety of other pathological states, and I have recently studied tissue from an instance of chronic lead intoxication in which pericapillary beading was identical to that seen in Sturge-Weber-Dimitri syndrome. Calcification of the brain also occurs in hypoparathyroidism, and, in a recent extensive review of the subject by Sugar,[15] the localization of the calcification was chiefly in the basal ganglia, the cerebellum, and the cerebral white substance. Roentgenographic evidence of linear calcifications outlining the cerebral convolutions in persons with port-wine nevi of the face permits a positive identification of Sturge-Weber-Dimitri syndrome.

SUMMARY AND CONCLUSIONS

The clinical and pathological features of Sturge-Weber-Dimitri syndrome are reviewed.

The anatomical basis for this syndrome is a hemangiomatous dysplasia in the cephalic region.

The cardinal clinical features of the syndrome are a vascular nevus of the face associated with signs of cerebral dysfunction, such as epilepsy, mental deficiency, and hemiplegia, and roentgenographic evidence of sinuous shadows within the cranial cavity.

The superficial hemangiomatosis may be limited to the face or scalp but may also involve the uveal tract and the conjunctiva, as well as the mucosa of the mouth, nose, and throat.

The intracranial hemangiomatosis is generally restricted to the leptomeninx covering the cerebral cortex, but minor foci of hemangiomatosis may be found within the cerebral cortex and in the subcortical medullary substance.

The cerebral cortex underlying the leptomeningeal hemangiomatosis exhibits two distinct types of histopathological alterations, namely (*a*) complete or almost complete deficit of nerve cells with extensive gliosis and obliterative pericapillary fibrosis, and (*b*) pericapillary beading and sheathing, as well as spherical and mulberry concretions within the nerve cell layers with disorganization of the cytoarchitecture and gliosis.

The pathogenesis of the cerebral cortical changes is probably disturbed metabolism, induced by the venous stasis in the increased number of pial veins. If the extreme metabolic disturbances occur very early, there may be complete loss of nerve cells with reactive gliosis and little calcification. If the metabolic disturbance brought on by the stasis is gradual in development, calcification and/or ferrugination may occur.

The metabolic disturbance induced by the excessive vascularization of the medullary substance results in regional gliosis, tissue degeneration, and calcification.

The double contour radiopaque lines seen in roentgenograms outline the cerebral convolutions, and not calcified blood vessels. These lines are not pathognomonic of Sturge-Weber-Dimitri syndrome, being found in other disorders in which the metabolism of the cerebral cortex has been altered.

The clinical and roentgenographic changes may be progressive, whereas the primary hemangiomatosis is probably not a proliferative process.

Drs. John Maloney and Carl Rosenberg gave valuable assistance in obtaining the material for this study.

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AMORPHOSYNTHESIS FROM LEFT PARIETAL LESION

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THE DIFFERENCE between the disturbance of recognition produced by lesions of the left parieto-occipital region and that resulting from a similar lesion of the right side has been discussed by many authors. Varieties of agnosia usually result from a left-sided lesion, whereas damage to the right side commonly leads to lack of recognition of the left side of person and extrapersonal space, and, in a few instances, to spatial disorientation and topographic agnosia. Lange,[1] Dide,[2] Lenz,[3] and McFie and associates,[4] in noting the frequency with which disturbance of perception of spatial relationships follows right parietal lobe lesions, have proposed that the right hemisphere has some particular function in regard to spatial perception.

Denny-Brown, Meyer, and Horenstein [5] have recently proposed an alternative view. From an analysis of a particularly clear-cut example of a right parietal lesion with disturbance of dressing and disregard for the left side of space, these authors conclude that such disorders are the result of a defect in spatial summation, without the need to postulate any disturbance of body image or of any special sense of space. Defect in spatial summation was found to be apparent in even the simplest types of sensory disturbance resulting from a parietal lesion. They are seen, for example, in the errors in perception of temperature, touch, and pain and in two-point appreciation. The more extensive the parietal lesion, the more extensive is the disorder of spatial perception. Imperception of parts of the body and of extrapersonal space is viewed as the full extent of disturbance of parietal functions, which, in less degree, was represented only as tactile and visual extinction. This disorder of the physiological process of spatial summation was called "amorphosynthesis" and is strictly contralateral to the damaged parietal lobe. A sharp distinction was drawn between this type of disorder and true agnosia, which is a disorder of perception of symbols and concepts and applies to both sides of space as a result of damage to one (dominant) hemisphere.

According to this view, all the disorders which comprise amorphosynthesis should occur only on the side opposite the lesion and should be present on the right side from left parieto-occipital lesions of sufficient severity. Whereas the simpler kinds of amorphosynthesis are frequently observed in cases with left-sided lesions, the more complex are thought to be obscured by the commonly associated aphasia and agnosia. The occasional occurrence of topographic agnosia in association with

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right parietal lesion (Paterson and Zangwill [6]; Nielsen [7]; McFie, Piercy, and Zangwill [4]) suggests that the right parietal lobe can be dominant in at least some respects. If this is true, such patients must have a nondominant left parieto-occipital region. It is therefore remarkable that the disturbances classed as "amorphosynthesis" should seldom have been reported on the right side as a result of left parietal lesion. We wish to discuss the following case presenting some features of right amorphosynthesis of severe degree.

REPORT OF A CASE

History.—W. F., a 36-year-old white married boiler maker, was admitted to the Boston City Hospital on March 23, 1953. He had no complaints on admission, stating only that his doctor wanted him hospitalized. He had been well until one week prior to admission, when generalized weakness and malaise were noted. Three days prior to admission a bilateral frontal dull throbbing headache occurred. These symptoms persisted. On the day of admission, when suddenly rising rapidly from bed, he developed right-sided weakness and right facial asymmetry. He attempted several times to walk but collapsed each time, unable to support himself, and was referred to the hospital.

This patient has always been right-handed. Smoking, writing, eating, throwing, and batting have always been with his right hand. Sighting has been with his right eye. There are no known left-handed relatives.

On admission to the medical service, his vital signs were normal, and cardiac rhythm was regular, with a Grade 1 apical systolic murmur. He was oriented as to time, place, and person but was lethargic and tended to sleep whenever there was a pause in the examination. He repeatedly threw his right arm away, saying that it didn't belong to him. When he was answering questions, his head was tilted backward and head and eyes were turned to the left, as if talking to someone at the head of his bed on the left side. He had no aphasia. The left pupil was 4 mm. and the right, 3 mm. in diameter; both reacted to light and in accommodation. There was a right central facial weakness. His gait was unsteady, with a tendency to fall toward the right. It was difficult to get him to use the right limbs, and the movements, when made, were weaker than those of the left side. All simple movements of the right limbs could be performed, however. The right limbs were almost completely flaccid. The tendon reflexes were slightly more active on the right. Both plantar responses were flexor. The patient denied feeling pain, temperature, or touch on the right half of his body and said, "How can I when it doesn't belong to me?" He continued to throw his right arm from the bed stating, "It must belong to someone else." When he was being helped into a hospital gown, he became agitated and refused to put his right arm into the sleeve. Again he denied that extremity. This behavior was also present the following morning. At that time he was oriented in all spheres, but simple calculations were done poorly. He was unable to read words printed horizontally, but vertical columns of words on the left side of the paper were read correctly. He was able to identify his fingers. Although he misidentified the examiner's right and left, he did not confuse right and left on his own body. He had no difficulty in naming objects and was able to understand oral commands.

On his second hospital day the patient was transferred to the neurological service for further investigation.

Examination.—The blood pressure was 130 mm. Hg systolic and 80 mm. diastolic. Temperature, pulse, and respirations were normal. General physical examination was normal. Sensation to touch and pain was slightly diminished over the right side of the face. Bilateral facial stimulation was described as a single stimulation on the left. There was weakness in movement of the lower parts of the face on the right side. Weber and Rinne tests were normal; but with simultaneous vibration to each ear, only the left was reported. The other cranial nerves were normal.

On the first day of illness, it was difficult to demonstrate full strength of dorsiflexion of the right wrist, and the whole arm tended to drift laterally when extended. The individual fingers assumed uneven degrees of extension. From the second day onward the patient, with encouragement, made any requested movement of the right limbs with full strength. During examination the right fingers and the entire hand tended to overextend involuntarily. This was most

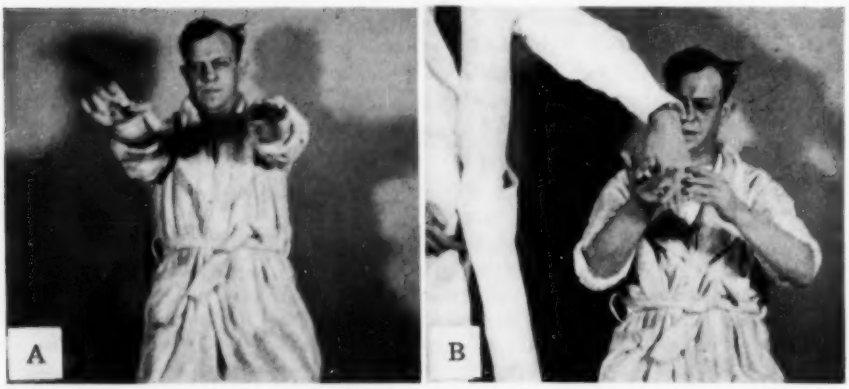

Fig. 1.—Abnormal postures in the right hand in the patient, W. F.: (*a*) when outstretched; (*b*) when asked to take hold of any object with both hands.

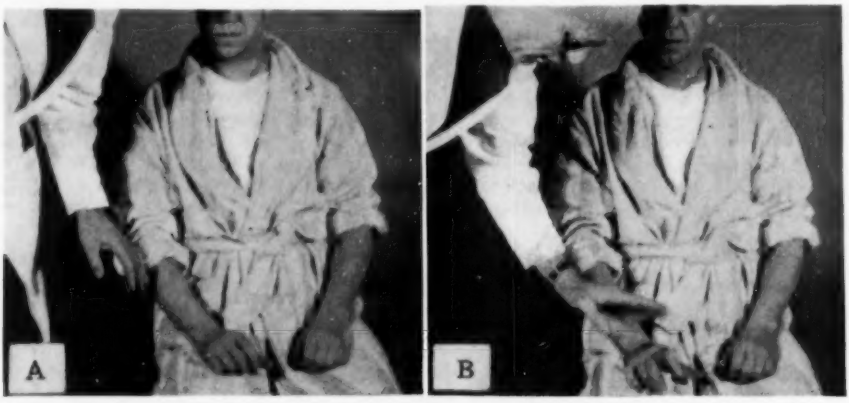

Fig. 2.—Involuntary extension of the right hand of the patient as the examiner's hand approaches it.

Fig. 3.—Overextension in the right hand during the early phase of grasping movement.

prominent with the arms outstretched (Fig. 1*a*) but was also noticeable in movement (Fig. 1*b*). Tactile stimulation over the dorsal aspect of the right hand, whether at rest or held outstretched, led to further extension of the fingers and wrist (Fig. 2*a* and *b*). During a grasping movement the fingers were overextended (Figs. 3*a* and *b* and 1*b*). There was no weakness in movement or abnormal posture in the right lower limb. His gait was normal. He used his left hand in eating. Although his right hand was heavily tobacco-stained, he then held a cigarette in his left hand. Rapid rhythmical movements were performed more slowly and awkwardly on

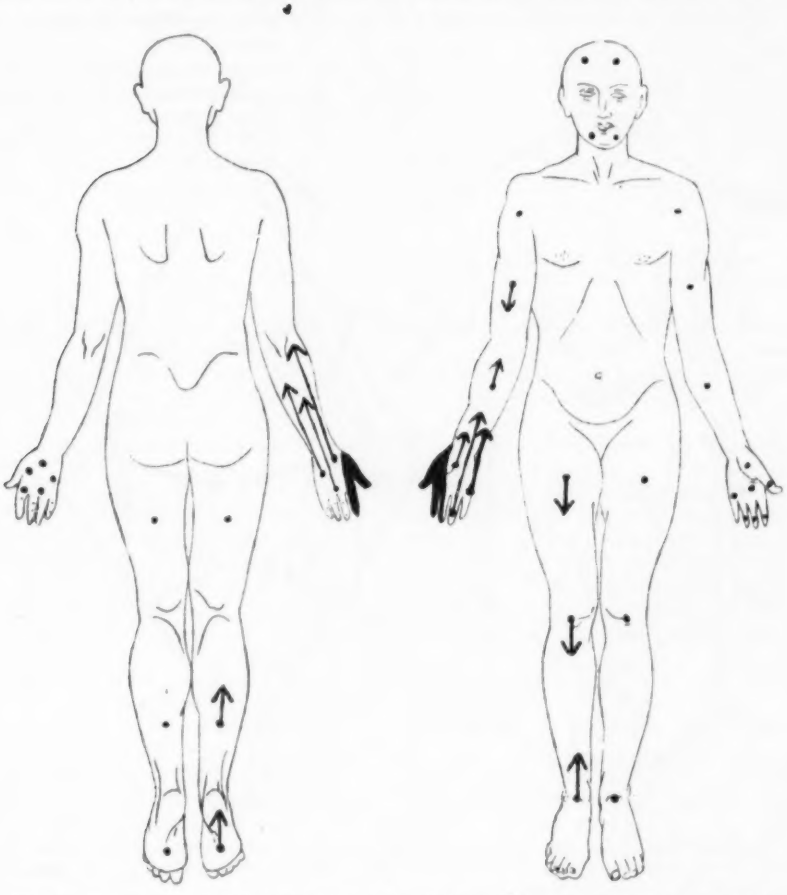

Fig. 4.—Extent and direction of errors in tactile localization in the right arm and leg in the patient, W. F. Where no arrow is shown, localization was correct. There was no perception of contact in the black area on the radial border of the hand.

the right, but rhythm was not impaired. The patient could scribble his name and express himself in writing with his left hand. However, when he attempted to use his right hand, the pencil was placed awkwardly in the hand and with pencil pointed in the air he wrote with his fingernails. He made appropriate movements, but the pencil rarely touched the paper. He appeared surprised that only a few marks on the paper resulted. When combing his hair, the right fingers ran through the hair while the comb pointed into space. He shaved only on the left side of his face, and this was done rather awkwardly with his left hand. He did not

notice this, but when his attention was drawn to it, he explained it by an inability to use his left hand for shaving. This unilateral shaving persisted whenever he attempted to shave himself throughout his hospital stay.

After the second day the abdominal, biceps, triceps, radial, patellar, and Achilles tendon reflexes were equal, and the plantar reflexes were flexor.

Sensory examination revealed that the patient perceived pain, temperature, touch, and vibration, but on the right the sensation was described as "not as clear" as on the left. On the radial aspect of the right hand, there was thermal, pain, and tactile loss even to broad hot and cold objects, several points, and heavy contact (Fig 4). On bilateral stimulation the

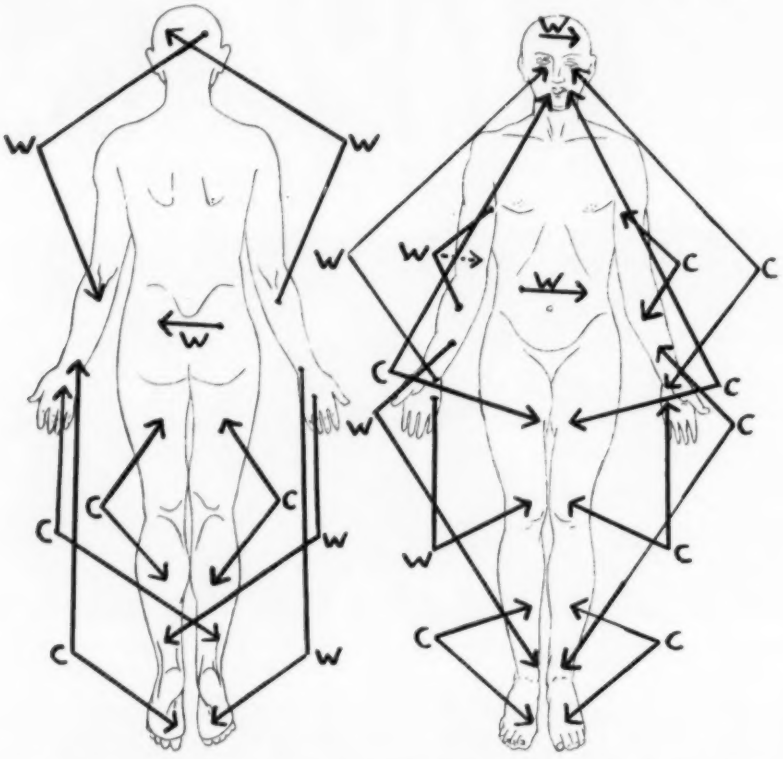

Fig. 5.—Errors in the appreciation of double stimulation. The arrow heads indicate the location of the resulting perception. *C* indicates that both stimuli are perceived; *W* indicates extinction of one of the two stimuli.

patient could not perceive pain, temperature, touch, or vibration on the right. This extinction varied. Usually it was complete for the right half of the body. Sometimes the right leg and the right side of the face were spared. Stereognostic sense was absent in the right hand, and the patient was not able to recognize skin writing over the right hand and forearm. By use of the compass test with blunt points, it was obvious that he was unable to recognize two simultaneous stimuli over the right hand and distal forearm, no matter how far apart the points were separated. When two points were stimulated on the right side of the body, the face was "dominant" over the arm and leg, and the leg over the arm, during the first week. Thereafter stimulation of the face and leg was recognized as double. Stimulation of any point on the left side could dominate any stimulus on the right side, with the exception of the right leg (Fig. 5).

There were no errors on the left side. Tactile localization at first was grossly erroneous over the right hand, arm, and leg, but after one week consistent errors were made only on the right hand and distal forearm (Fig. 4). This area was more extensive than the radial area of sensory loss. Position sense was absent in the right fingers, impaired at the wrist, and reduced for only a few days in the toes. In the proximal joints it was accurate.

Special Tests.—After the patient's second day in the hospital he was able to read. He realized that his arm belonged to him and recalled trying to throw it away. He laughed when reminded of this. He was oriented in space, knowing directions about the ward, and was able to hold a stick horizontally or vertically on command. He continued to have difficulty in dressing during his entire hospital stay. He made only a slight gesture of his right hand toward his right sleeve and then continued as if the arm had been clothed. He identified right and left on another person correctly after the fourth day. Even on the 12th day he would put the right elbow into the sleeve of a garment and, after properly putting his left arm in the left sleeve, would drape the rest of the garment around his right side. He did not appear to notice that the right arm was uncovered. Later, he was aware of this difficulty and he related it to an inability to direct his right hand in space. There was no evidence of an aphasia. The patient always expressed himself clearly and had no difficulty in naming objects. He was able to draw and copy from memory reasonably well with his left hand. The copy of a diagram was usually erect, but occasionally the lines would slope a little to the right. His writing with his left hand had no abnormal slope and was fairly legible. He had no difficulty in finding his way about the ward, and maps of the city, state, and country were drawn well. He was able to bisect lines and indicate the midpoint of a circle accurately. The right attention hemianopsia could be eliminated by increasing the size of the stimulus. There was never any evidence of an inability to identify parts of his body, of confusion as to left and right on his own body, or of finger agnosia. The mirror-image identification on another person ceased after the first two days of hospitalization.

Laboratory studies revealed normal urine and a persistently elevated white blood cell count, ranging from 10,000 to 14,000 cells. The differential count was normal, and no atypical cells were present. There was no anemia. Corrected sedimentation rate and platelet count were normal. The blood Hinton test was negative, and the blood urea nitrogen was 17 mg. per 100 ml. Lumbar puncture on admission revealed an initial pressure of 150 mm. of water; clear, colorless spinal fluid with 2 lymphocytes per cubic millimeter; a normal colloidal gold curve, and a negative Hinton test. Two weeks following admission the lumbar puncture was repeated, with the same findings except for a positive Pandy test and a total protein of 60 mg. per 100 ml.

Electroencephalograms were obtained on admission and one week later. These contained low-potential fast activity. On the first record there were focal slow waves in the parietal and occipital leads on the left. With hyperventilation rambling medium-potential 2-cps delta rhythm was seen bilaterally. This was most striking on monopolar leads referred to the left ear. The first record was interpreted as mildly abnormal, with a focus in the left parieto-occipital region.

An electrocardiogram was within normal limits. Chest and skull x-rays were normal. A pneumoencephalogram showed symmetrical ventricles of normal size, with the third ventricle in the midline. Arteriograms were made with injection of the left and right common carotid arteries. Vascularity was increased in the left posterior parietal area, but not of a degree sufficient to warrant a neurosurgical exploration, particularly as the patient was steadily improving.

Course of Illness.—The patient was observed in the hospital for three weeks and followed in the outpatient department for three months. At the time of discharge from the hospital his right facial weakness had disappeared, but the sensory ataxia of the right hand was so marked that it resulted in his losing his job as boiler maker and necessitated a change of occupation. After three months he was beginning to write, shave, and eat with his right hand again. He no longer neglected the right side. The tendency to overextend the right fingers and wrist when the hand was examined still persisted. Position sense in the fingers on the right was reduced but not absent at that time. Astereognosis and the sensory extinction were still noted on the right. Hypalgesia and hypesthesia were present over the right hand and distal forearm. Tactile localization and two-point discrimination were poor in that area.

Clinical Diagnosis.—The clinical diagnosis was a left anterior parietal lesion, probably a small hemorrhage from a vascular anomaly.

COMMENT

This patient presented the sudden onset of signs characteristic of a left cortical parietal lesion. Besides loss of position sense, two-point discrimination, and tactile localization in the right limbs, there was astereognosis, visual inattention, defect in dressing and shaving on the right side, and, initially, a denial of the right limbs and denial of illness. There was no aphasia or agraphia and no difficulty in the visual recognition of objects or of directions in space. There was an initial, very transitory difficulty with simple calculations, but no trouble in identifying parts of the body was found. The only confusion of right and left was his speaking of the examiner's limbs as if they represented a mirror image of his own.

Except for a small area on the radial side of the right hand, the ability to perceive touch, pain, temperature, and vibration was intact. This area of deep loss of these elementary sensations indicates damage to some fibers of the sensory thalamocortical radiation, probably in or near their entry into the parietal cortex, for there was no reason to suspect the presence of thalamic or capsular lesion. The remainder of his disorder presents in the right limbs the disorder of perception we have named "amorphosynthesis" (Denny-Brown, Meyer, and Horenstein [5]) resulting from a parietal lesion. The symptoms and signs are those resulting from defective perception of the spatial aspects of all forms of sensation arising in the right side of the body. There is an associated vulnerability of such perception in rivalry with more clearly differentiated stimuli from the sound side. The resulting "extinction" was apparent in relation to pain, touch, temperature, and vibration sense, as well as visual stimuli in the right half-field. There was little evidence of visual amorphosynthesis. He could mark the center of lines and figures, copy diagrams and drawings reasonably well with his left hand, and estimate distances well. His writing and designs did not even show any displacement of axes and coordinates of the type discussed by Paterson and Zangwill,* Lenz,[3] Bender and Teuber,[9] and others. Yet the ease with which extinction could be demonstrated in the right visual field and his reading difficulty indicated that a minor degree of visual imperception of the same kind existed and persisted throughout the period of observation.

Except for some difficulty in simple calculation on the first day of hospital admission, our patient showed no defect in recognition or mental manipulation of conceptual symbolic data. Objects and parts of the body were readily identified except by palpation with the defective right hand alone. Such "astereognosis" is only part of amorphosynthesis. Nevertheless, the initial denial of the right limbs, or any disability, and the persistent ignoring of the right side in dressing and shaving indicate a more extensive defect in behavior than might be expected from the degree of perceptual difficulty. Unawareness of hemiplegia was originally described by Pick,[10] and Anton [11] emphasized this peculiar failure of perception with special reference to blindness. Babinski [12] called unawareness of hemiplegia an anosognosia, and in the ensuing discussion Henry Meige suggested that anosognosia was secondary to lack of recognition of the limbs, whether paralyzed or not. Pinéas [13] showed that anosognosia was regularly associated with sensory loss of cortical type, though this was not necessarily severe. These phenomena have frequently been related to loss

* References 6 and 8.

of part of a conceptual entity, the body image.† Apraxia of dressing was described by Brain,[15] in 1941, as a disorder of body scheme, and its appearance was noted with the severer degrees of disorder of space perception which he termed "agnosia for the left half of space as such." Others have related disorder of dressing to impairment of visuospatial judgment (Hécaen and de Ajuriaguerra [16]; McFie, Piercy, and Zangwill [4]).

Our patient could picture to himself his right limbs. He behaved and spoke as if no particular situation or happening was present on his right side. He usually looked to his left and gave only rare glances to his right. Yet his attention could be directed to the right, and his visuospatial judgment was as good to the right as to the left. He was not disoriented in space. We, therefore, could not demonstrate any defect in his visuospatial perception except for the most minimal degree represented by "visual inattention." All the symptoms in our patient relate to a neglect of the right side of the body; yet his concept of his body and its parts was unaltered. The symptoms improved as the degree of unawareness of the right side improved. For a period when these symptoms fluctuated, the disorders of more elementary sensation also fluctuated, and such variation could be shown to be due to the operation of "extinction," by which perception of an event on the right side suffered in competition with events on the left side. Denny-Brown, Meyer, and Horenstein [5] found that the phenomenon of extinction of a touch or a pinprick was related to defective spatial summation, and hence poor differentiation, of the extinguished stimulus, in competition with a more highly differentiated stimulus. If a single stimulus can be extinguished in this way, it is clearly possible that multiple stimuli from the affected region, such as accompany contact with large objects, are also vulnerable in competition with similar stimuli arising in normal areas. We therefore believe that failure to perceive that a limb is unclothed, or the hair on one side of the head is in disarray, or the face is unshaved, is another aspect of the phenomenon of extinction. Thus, perception of existence of a limb, or disability of it, can suffer extinction if the spatial disorder is sufficiently extensive, and if the normal side provides highly differentiated sensation of its presence. In our patient, behavior was continuously oriented to the left side in the beginning and intermittently neglected the right side in convalescence.

The disturbances classed as amorphosynthesis include all one-sided manifestations under this heading. Disorders in the formulation or use of symbolic concepts, including the names of parts of the body, the names of objects, and the significance of numbers, of topographic scheme or plan, and in the utilization of such concepts are included under agnosia. True agnosia applies to both sides of person or of space and results from a lesion of only one hemisphere, that which is dominant. Disorder of spatial localization, for example, is either right- or left-sided and occurs contralateral to the lesion.[17] It is therefore a manifestation of amorphosynthesis. Topographic agnosia is a generalized inability to visualize a plan or route and is a true agnosia. Hitherto the more complex types of amorphosynthesis have been confused with agnosia; or the complex types of amorphosynthesis have been thought to result from damage to the "minor" hemisphere, and agnosia, from the "major" side. Schilder [18] reported a right-handed patient with apoplectic onset of right hemiplegia and loss of tactile localization, discrimination, and posture. Marked sensory impair-

† References 2 and 14.

ment for touch, pain, and temperature was described. While observed in the hospital, she frequently denied her right extremities and her right hemiplegia. This patient was considered to be an unexplained exception to Babinski's rule that right-hemisphere lesions produce anosognosia. Hécaen and de Ajuriaguerra [16] reported a right-handed patient with two left-hemisphere bullet wounds who had "an agnosia for the right half of body." He thought his right arm and hand were missing. He was able to identify right and left on his body but not on the observer. An apraxia of dressing and a difficulty in copying designs were present. There was no evidence of autotopagnosia, digital agnosia, or aphasia. The defect was thought to be related to a type of spatial agnosia. Nielsen [19] reported a right-handed patient who had the sudden onset of right hemiplegia, delusion of absence of the right arm, and anosognosia. Agraphia, "finger aphasia," allochiria, and constructive apraxia were noted. Position sense was absent on the right. Because this patient had no history of left-handedness, it was postulated that the dominant hemisphere contained both the major and the minor areas.

These cases, and the one reported here, indicate that the lack of recognition of the opposite side of person, anosognosia, and disorder of dressing can occur with left, as well as right, parieto-occipital lesions. Yet, even in severe right parieto-occipital lesions, disorder of dressing and anosognosia are not always present. Hécaen, de Ajuriaguerra, and Massonnet,[20] in reporting five cases of right parieto-occipital lesion with visual field defect and with disturbances of drawing and copying figures, comment on the absent or minimal disorder of dressing in their cases. They maintain that disorder of dressing tends to be associated either with predominantly "visuoconstructive" disorders, such as defective drawing or route finding, or with right-left disorientation (planatopokinesis). Right-left disorientation is complicated by the presence of extinction, and the presence of visual field defect further obscures the validity of this division of parietal lobe disorders into two types.

The case reported by Denny-Brown and associates [5] showed that disorders of visuospatial synthesis are independent of field defects, and we believe they result from damage to the parietal lobe. These authors view the function of the parietal lobe as uniformly concerned in spatial synthesis, with emphasis upon disturbance of somatic or visual functions being determined by the degree to which incoming bodily or visual sensations are prevented access to the remaining parietal function. If cortical function is viewed as a reaction to all the factors arising in the environment, acting through the displacement of body parts, as well as through the exteroceptors, the neglect of body and of functions connected with the body may be expected to follow damage to the region of influx of bodily sensation. Neglect of extrapersonal space would then be attached to disorder primarily involving visual factors. We find that incomplete disorders indeed tend to involve chiefly either personal or extrapersonal space.

Visual disorientation (Brain [15]) and other visuospatial disorders (Paterson and Zangwill [6]) have been previously reported from left parieto-occipital lesions. The persistence of extinction in the visual half-field in our patient and its initial severity indicate that, though the disorders chiefly affected behavior relating to the patient's own body-half, the parietal type of visual perceptual disorder was, nevertheless, present in some degree. In this patient the type of sensory disorder indicated damage to the anterior parietal region, with some damage extending to the postcentral gyrus (severe sensory loss in the radial border of the hand). We therefore

consider "anosognosia," denial of the limbs of one side, and "apraxia of dressing" to be the severest degree of loss of that part of parietal function which relates to bodily sensation. In contrast, visual inattention, defective copying of designs, distortion of visual coordinates, errors in visuospatial judgment, loss of spatial localization, and denial of blindness represent successively greater degrees of severity of the visual component of parietal lobe function.

We would stress once again that amorphosynthesis is a disturbance in cortical function manifest as a disturbance of behavior. Its sensory qualities are revealed only by special testing. On this basis, denial of disability, behavior as though the limb belonged to another, and unilateral neglect of dressing are the primary disorders in cortical function. Analysis of the attitude of the patient toward these symptoms and his statement of what he perceives introduce secondary factors.

Corresponding to this defect in behavior, resulting from loss of cortical stimulus function, there is a release of remaining cortical function. Release was apparent in the present patient in two respects. In the beginning, whenever he was addressed, he turned his bead upward and to the left in replying, as if to speak to a person standing at the head of the bed on the left side. From the third to the seventh day he tended to look only to the left, and after that time his head and eye postures were natural. Secondly, at the onset the right arm was held flexed with extended fingers and wrist whenever he was examined; otherwise it lay limp and in natural posture. From the third day onward for more than three months the fingers and wrist of the right hand were held in unnatural extension whenever he was asked to hold them outstretched. We have described elsewhere ‡ this "levitation" resulting from parietal lesions. Stroking contact with the hand elicited the same posture. In the course of approaching an object to grasp it with the right hand, this overextension was constantly exhibited. This is an unconscious posture, independent of "sensory ataxia," and is related by us to release of an "avoiding reaction" on the affected side. It is not present with a lesion of the postcentral gyrus alone, even if loss of position sense in the hand is complete. It is the opposite of the instinctive grasp reaction and is released by parietal lesions (which abolish the grasp reaction). These abnormal postures document the release of function of the remaining hemisphere (adversive) and of the remaining parts of the damaged cerebral hemisphere (avoiding). The peculiar, naïve explanation offered by these patients for their behavioral defect is itself part of the defect in behavior, reflecting a further unawareness of inconsistencies in discussion about the affected side.

Schilder concludes that denial of disability is an unconscious repression of the unpleasant fact of disability. He termed it an "organic repression" because the unconscious wish had a basis in organic disability. In our own patients we find no reason to set anosognosia apart in this way. The denial of disability is not different from the denial of ownership of the limbs or of the defect in dressing, and the explanation given for each by the patient is equally inadequate. He does not appear to be interested as to why "an arm of the patient in the next bed" is lying across him, whether or not he has a hemiplegia. He does not wish to discuss the affected side or finds it difficult to focus his thoughts upon it. An extraordinary case of anosognosia for hemiballismus reported by Roth,[22] when asked about the movements of the affected limb, said, "I don't understand it. I just heard about it this last

‡ References 5 and 21.

week. I don't know about moving this left hand. That's something new. I couldn't tell you. If I do, I don't realize it." Such replies appear to us to indicate a mental aversion rather than a repression, a mental "avoiding response" comparable to the motor reaction of the hand and allied to the peculiar retracting avoiding reactions we have found in the monkey with parietal lesion. In this sense, reason and judgment are not mental functions separate from any somatic counterpart, but within each sphere of interest are intimately related to their physiological behavioral substrate.

The occurrence of the phenomena of amorphosynthesis in the right limbs of a right-handed patient, without disorder of the conceptual functions we have called true agnosia, raises two possibilities. First, the right hemisphere may be dominant in the patient, so that in him a left parietal lobe lesion produces the defect usually presented by the minor side. Though we are unable to deny this possibility, it has also to be borne in mind that the postulated lesion, involving the more anterior part of the parietal lobe, should spare the juxtaoccipital region usually implicated in visual types of agnosia. A second possibility is, therefore, that the lesion did not extend posteriorly to produce agnosia. This appears to us to be the more likely, because transitory difficulty in simple calculation was present on the first day. Five months after illness reported in this paper our patient had a further mild transitory attack of mental confusion, with renewal of loss of discriminatory sensory function in the right limbs. Some difficulty in naming objects and mild semantic dysphasia for two days on this occasion gave further evidence that his left hemisphere is dominant. Fragments of the transitory syndrome presented by our patient are commonly seen in states of confusion associated with true agnosia resulting from larger left parieto-occipital lesions. We therefore believe that the paucity of published cases of right-sided amorphosynthesis is due only to the fact that they are seldom seen in uncomplicated form.

CONCLUSIONS

The unilateral disorders of recognition of the opposite side of the body and of space resulting from parieto-occipital lesion described as amorphosynthesis can occur as a result of left-sided lesion. In the absence of aphasia and conceptual agnosia, they do not differ from the more commonly observed result of a right parietal lesion. It is concluded that in such cases the defect in behavior is the result of ineffective sensory synthesis by the parietal lobe, with consequent loss of cortical stimulus value from the opposite sensory fields in the motivation of behavior.

Anosognosia, denial of limbs, and apraxia of dressing are not true agnosias. They are the result of maximal degree of somatic amorphosynthesis and may be either right- or left-sided. They appear when somatic, bodily factors in sensory synthesis are severely impaired, and are not part of defective visuospatial, extrapersonal synthesis.

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CHRONIC ANXIETY SYMPTOMATOLOGY, EXPERIMENTAL STRESS, AND HCL SECRETION

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PREVIOUS experiments demonstrated significant increases in HCl secretion during experimentally produced chronic fear in dogs and monkeys * and during sustained "examination-period anxiety" in undergraduate students.[11] Indices of the HCl secretion of a chronically anxious patient were higher during five very anxious psychoanalytic hours than during five relatively nonanxious hours.[13] Other investigators, largely in studies of single subjects, have reported similar results.† Evaluation of those studies reporting a negative ‡ or a variable relationship [17] between HCl secretion and anxiety is hindered by a lack of either adequate experimental controls or sufficient data. These studies have been discussed in more detail elsewhere.§ The primary interest of this report is the implication of these results for the unqualified use of Cannon's [5] emergency theory of emotions as a basic concept in psychosomatic theory.

The apparently consistent finding of increased HCl secretion during sustained anxiety in controlled experiments is just the opposite of what one would expect if the extension of Cannon's theory from acute-emergency to chronic emotions || were valid in psychosomatic theory. According to this position, in both acute and chronic anxiety there is sympathetic-epinephrine excitation and parasympathetic inhibition. Thus, vagus-excited increased HCl secretion should not be a component of either acute or chronic anxiety. Several proposals have been made to resolve the contradiction between this conclusion and the experimental findings cited above.

Alexander [1] and Szasz [16] have assumed that the dogs in the study referred to above [10] were not primarily frightened but were primarily regressed. They believe that the concept of "vegetative retreat" adequately accounts for the findings. It has

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* References 10 and 12.

† References 2, 7, 9, 14, 15, and 18.

‡ References 3 and 6.

§ References 11 and 12.

|| References 1 and 4.

been shown,[11] however, that the animals anticipated painful shock stimulation with avoidance behavior, developed phobic avoidance of their cages where the experimental stimulation occurred, trembled and startled to extraneous stimuli—in short, behaved in a manner usually considered to be motivated by fear. Increased HCl secretion accompanying this behavior was also associated with increased heart rate. In the subsequent study with monkeys, independent judges agreed that their behavior was "fearful" at the times HCl secretion increased. Blood sugar measurements in these animals showed no hypoglycemic changes interdependently related to the increased HCl secretion or the behavioral changes.

Not only is the skeletal behavior of the dogs and monkeys contrary to the "withdrawal from action" of the vegetative-retreat principle, but the multiple autonomic changes do not support the picture of a generalized shift from predominantly sympathetic-epinephrine to vagus-insulin excitation hypothesized in this principle.

One of us (G. F. M.) once proposed [10] that HCl secretion during fear may have been erroneously subsumed under the emergency theory. This suggestion was made because the total amount of data on HCl secretion considered by Cannon [3] was limited and only one observation (Le Conte's) seemed clearly to be of secretion during fear. Although not yet ruled out in human HCl secretion by experimental evidence, this suggestion now seems less likely than the following.

Exploratory observations in the study with dogs suggested that increased HCl secretion was associated with chronic, but not with acute, fear. The experiment with monkeys systematically investigated the nature of HCl secretion during acute-episodic and sustained fear. It was found that HCl secretion did not increase during brief fear episodes but that it did during relatively continuous, sustained fear. Both animal studies showed that mere repetition of discrete pain-fear stimulation and response was not sufficient for the appearance of increased gastric acidity. HCl secretion increased only when continuous, sustained fear developed or when sudden conditioned fear was evoked after sustained fear had been learned in response to a stimulus pattern and not extinguished.

The results of the two animal studies support the hypothesis that increased HCl secretion is associated with sustained or chronic anxiety but not with acute anxiety. This hypothesis directly implies that the extension of Cannon's emergency theory to chronic anxiety is not valid and thus resolves the contradiction stated at the onset of this discussion.

In a reinterpretation of the results of studies of human HCl secretion it was found that the majority of them agree with the above hypothesis.[12] An attempt to study this hypothesis directly in humans seems desirable, however, because none of these studies had systematically controlled the acute-chronic anxiety variable.

Aside from this theoretical goal, it also seems important simply to obtain more empirical data on HCl secretion and emotions in humans. Varying etiological importance has been attributed to dependency conflict, hostility, anxiety, and HCl secretion in peptic ulcer development. Yet there has been only one study in humans of anxiety and HCl secretion that included in itself more than one subject, control measurement, and a quantitative analysis of the reliability of the findings. There has been no published study of dependency conflict or hostility and HCl secretion meeting these minimal criteria.

The reader will soon discover that this experiment failed in its attempt to test the acute-chronic hypothesis in humans. The write-up follows the original prospectus of the experiment, however, to clarify the description of the study and certain methodological problems encountered.

PRESENT EXPERIMENT

I. *The Problem.*—The theoretical problem is to test in humans the validity of the hypothesis that HCl secretion does not increase during acute, but does during sustained, anxiety.

The ideal condition for testing this hypothesis is one in which the experimenter can control the variation from acute to sustained anxiety by manipulating the anxiety-evoking stimuli and the conditions of learning that determine this change. This is possible to a large degree in experiments with lower animals [12] but is not feasible in the majority of conceivable human studies.

An alternative procedure of "controlling" the acute-chronic anxiety variable determined the design of this experiment. The intent was experimentally to induce anxiety responses for a brief period of time in a group of already "chronically anxious" people (experimental group) and in a group of subjects not reacting with sustained anxiety (control group) up to the moment of the experimentally induced anxiety episode.

If these conditions are met and the acute-chronic hypothesis is valid, one would predict the following:

(*a*) Independent of the experimental anxiety condition, the gastric acidity of the experimental group will be significantly greater than that of the control group. This would demonstrate further that chronic anxiety and HCl secretion in humans are positively related.

(*b*) The gastric acidity of the control group will not increase during the acute experimental anxiety condition, and this secretory response will be significantly different than that of the experimental group. This would demonstrate that in humans acute anxiety is not accompanied by increased HCl secretion.

The procedure of the experiment cannot guarantee, however, that the intended differential pretest conditions of sustained anxiety would actually obtain between the two groups, but practically guarantees at least a difference in degree of pretest anxiety. In such a case, the effect of variation from acute to sustained anxiety cannot be tested, for there is no basal condition of no, or very slight, anxiety to change into a sudden, acute anxiety episode in the control group. Prediction (*a*) would still be made on the assumption that the positive HCl secretion-chronic anxiety relation is an increasing function and not simply an all-or-none relation. Some slight evidence from the monkey study already cited supports this assumption.

It is not possible to predict precisely the HCl secretory responses of the experimental subjects or of the control subjects if the latter anticipate the experimental stress with anxiety. If the interaction of the prestress and the stress-induced anxiety is cumulative, one would predict increases in HCl secretion during the experimental anxiety episode. But a cumulative interaction is not necessary, or the only possible, consequence here, and there is no adequate way available at present to measure such changes in the anxiety variable under these particular experimental conditions. The nature of these HCl secretory responses is left as an empirical subquestion of the study.

The experimental problem is to test the appropriate predictions and investigate the empirical subquestion cited above.

II. *Procedure.*—(*a*) Subjects: Before any one was accepted as a subject and tested under the experimental conditions, he was evaluated clinically to see whether he met a priori criteria for assignment to the experimental or the control group. The criterion for assignment to the experimental group was a presenting history of chronic anxiety symptomatology which included repeated subjective anxiety experiences and at least one of the group of physiological symptoms generally regarded as an indication of "free-floating" anxiety. The criteria for assignment to the control group were that the person was not undergoing psychiatric treatment at the time of the study and the absence of a history of chronic anxiety symptomatology.

The experimental group consisted of six psychoneurotic patients, five of whom were being treated as inpatients and one as an outpatient, and one person who was not a patient but who expressed some need for psychiatric treatment and whose life history was one of chronic anxiety reaction. The control group consisted of seven subjects who met the criteria. One of these had been under psychotherapy for a brief time but had interrupted it voluntarily two years before the experiment.

The clinical evaluation of the patients was based on the intake interview and additional material obtained during the course of therapy. The evaluation of the nonpatients was based upon one anamnestic interview and the subject's responses on a check-list questionnaire.

An attempt was made to match the control group with the experimental group with respect to sex and age. Each group contained five women and two men, but the mean age of the experimental group (36 years) is slightly greater than that for the control group (31 years). The influence of this factor will be assessed in presenting the results.

All subjects were first contacted about five days before the experimental sessions. At this time they were told that the study involved their "swallowing a stomach tube" and an investigation of their stomach secretions. The controls were also told that it would be necessary for them to be interviewed by one of the authors (E. B.), whom they knew to be a psychiatrist, and that the experimental sessions included a mild "stress" situation.

It was realized that the controls' foreknowledge of intubation, of the psychiatric interview, and of the use of a "stress situation" could produce anticipatory anxiety in them, maintain it up to the time of the experimental sessions, and so prevent the study of HCl secretion during only an acute-emergency anxiety episode. Yet experience with exploratory subjects convinced us that it was necessary to tell them these things to insure even the available source of controls, their cooperation as subjects, and freedom from contamination of the testing periods with strong affect evoked by the "surprise" of intubation. In order to reduce their anticipatory anxiety, the controls were reassured extensively about the procedures and were asked to consider the request for their services for two or three days before committing themselves.

During the interviews and the preparatory period on the first two experimental days, references by the controls to the pending experiment were noted. These observations form the basis for assessing whether or not the controls anticipated the experiment with anxiety, and thus which predictions could be tested.

(*b*) Measurement of HCl Secretion: Fasting gastric samples were obtained by aspiration through a Levin tube, which was introduced nasally in the majority of cases. The subjects had not eaten for a minimum of nine hours, or taken water for two hours, preceding any of the experimental sessions. The gastric samples were titrated against 0.1 N NaOH, using Töpfer's reagent and phenolphthalein as end-point indicators for free HCl and total acidity in the usual way.

(*c*) The Testing Conditions: With two exceptions, the subjects were tested under three different conditions on three successive mornings. In one exceptional case, one week separated the control from the remaining two conditions. In the other, an experimental subject left the hospital on the third morning and was tested only on the first two days.

1. Control condition, Day I: After the Levin tube was introduced, the subject lay quietly for five minutes. Then the stomach was "cleared" of residual contents.

The examiner then told the subjects that a buzzer would sound occasionally during the next period of time but that nothing else would occur. During the next 20 minutes a buzzer of 15 seconds' duration was administered in accordance with the schedule shown in Table 1.

At the end of this period all of the gastric contents that could be obtained was aspirated. Then a second, and final, 20-minute period ensued in which the buzzer was administered at the times shown in Table 1. At the end of this period a second gastric sample was obtained and the tube withdrawn. The mean of these two fasting samples was taken as the control condition gastric acidity measure for each subject.

2. Pain-pain anticipation condition, Day II: A 2 by 2 in. (5 by 5 cm.) area of the distal portion of the arch of the right foot was painted with India ink, and the foot was then so placed that it rested comfortably against the tip of a Hardy-Wolff-Goodell pain stimulator.[8] Immediately after intubation, a "pain-adjustment series" of buzzer and heat stimuli took place to establish the intensity of painful heat stimulation that would be used during the testing periods on this day. It was arbitrarily decided to use for each subject that intensity of heat stimulation producing rapid foot withdrawal on three successive stimulations.

A timing device was used whereby the buzzer was sounded for 15 seconds, and the shutter of the heat stimulator opened automatically four seconds before the end of the buzzer. A shutter

TABLE 1.—*Schedule of Experimental Stimulation* During the Two Twenty-Minute Test Periods*

First 20-Minute Period	Second 20-Minute Period
3′ Buzz-pain	4′ Buzz
7′ Buzz-pain	8′ Buzz-pain
10′ Buzz-pain	12′ Buzz-pain
13′ Buzz	13′ Buzz
14′ Buzz-pain	14′ Buzz-pain
18′ Buzz	18′ Buzz-pain

* On Day I and Day III only the buzzers were administered; on Day II the buzzers and the pain stimulation were both given.

opening of four seconds' duration was used throughout. At the end of this pain adjustment series, the stomach was cleared of its residual fasting contents.

Two 20-minute test periods then followed, as on the first day. But on this second day some of the buzzers were paired with the pain stimulus of the intensity established in the adjustment series. The actual sequence of buzzer and buzzer-pain stimulation is shown in Table 1. The subjects, of course, did not know which buzzers were to be paired with the pain stimuli. Gastric samples were obtained at the end of each 20-minute period, and the mean acidity of the two samples was taken for the acidity measure for each subject for this condition. The difference between the acidity of the first and that of the second day was taken as the HCl secretory response associated with the pain-pain anticipation condition.

3. Pain anticipation condition, Day III: The subject's foot was again painted with black ink and adjusted to the heat stimulator tip just as on the preceding day, but not as it was on the first day. The subject was again intubated and the stomach "cleared" five minutes later. During two subsequent 20-minute periods the buzzer was administered in accordance with the schedule of Table 1. No painful stimulation was given, but the subjects had no prior knowledge of this fact. Gastric samples were again obtained at the end of each 20-minute period. The mean of these two samples is taken for the gastric acidity measure for this condition for each subject, and the difference in the acidity of the first day and that of this day is taken as the HCl secretory response of the pain anticipation condition.

When questioned at the end of this condition, all subjects stated either that they did not know whether the "hot foot" would come on this day or that they had expected it to come. This shows that they did in fact anticipate the pain stimulation on this day, as intended by the experimental design.

The testing conditions of all three days also included the application of a blood pressure cuff to the right arm, a pneumograph to the trunk, and electrodes over the heart for the periodic measurement of blood pressure and the continuous recording of respiration and heart rates. (These multiple autonomic measurements are not reported here for the sake of clarity.)

III. *Results.*—(*a*) Anticipatory Anxiety of Control Subjects: Three of the seven controls indicated directly or indirectly in the psychiatric interview that they were concerned over having to "swallow a stomach tube." Five of the controls were judged to be apprehensive in the control condition, and six were judged to be apprehensive at the beginning of the pain-pain anticipation condition.

The increasing proportion of controls showing observable signs of anxiety as the time prior to the experimental sessions decreases is indicative of anticipatory

TABLE 2.—*Mean Gastric Acidity, in Clinical Units, on Control and Experimental Days*

Day	I. Control Day	II. Pain-Pain Anticipation Day	III. Pain Anticipation Day
Test samples	Total acid 19	29	34
	Free HCl 12	30	23
Clearing samples	Total acid 23	23	25
	Free HCl 12	12	14

N = 13. One subject (experimental group) who did not return for Day III has been omitted from this summary for clarity of presentation. Inclusion of her data for Day I and II increases the Day II-I difference and the reliability of this difference.

	Reliabilities of Test-Sample Differences		Reliabilities of Clearing-Sample Differences
	Total Acid	Free HCl	
I vs. II	$P < 0.02$	$P < 0.02$	All differences insignificant by inspection
I vs. III	$P < 0.01$	$P < 0.06$	
II vs. III	$P > 0.30$	$P > 0.40$	

Reliabilities of Net Differences Between Test-Sample and Clearing-Sample Differences

	Total Acid	Free HCl
I vs. II	$P < 0.02$	$P < 0.02$
I vs. III	$P < 0.01$	$P < 0.09$
II vs. III	$P > 0.30$	$P > 0.40$

anxiety that increases in strength as they approach the "goal" of the experimental sessions. The reality and strength of this anticipatory anxiety and its gradient nature are illustrated by the following observations: A control manifested little anxiety over intubation when first contacted but reported a "nightmare"—an event described by the subject as very unusual—the night before the first experimental session. Another subject indicated diffuse anticipatory anxiety in the preparatory period of the first day by asking whether he was to be shocked through the cardiac electrodes—after he had been told they were for picking up his heart beat—although this person was highly motivated to serve as a subject and was not observably upset when first contacted.

The judgments about the anticipatory anxiety of the controls were made prior to the stress situation, and thus independently of knowledge about the nature of the HCl secretory response during stress.

In view of these observations, one must conclude that the anxiety stimulation of the second and third experimental days was not of an acute-emergency nature for

the controls but interacted with their anticipatory anxiety reactions. Therefore, only prediction *a* and the empirical interest in the secretory responses of Days II and III are applicable. The latter is considered first.

(*b*) HCl Secretory Response to Anxiety Situations: The mean gastric acidity of both the control and the experimental group increased on Day II and Day III over the level of Day I. There were no significant differences between the two groups in their secretory responses of Day II or Day III. Consequently, the data of all the subjects are pooled for the most sensitive assessment of the HCl secretory response. These are presented in Table 2 and Chart 1. The mean gastric acidity of test samples during the pain-pain anticipation condition of Day II and

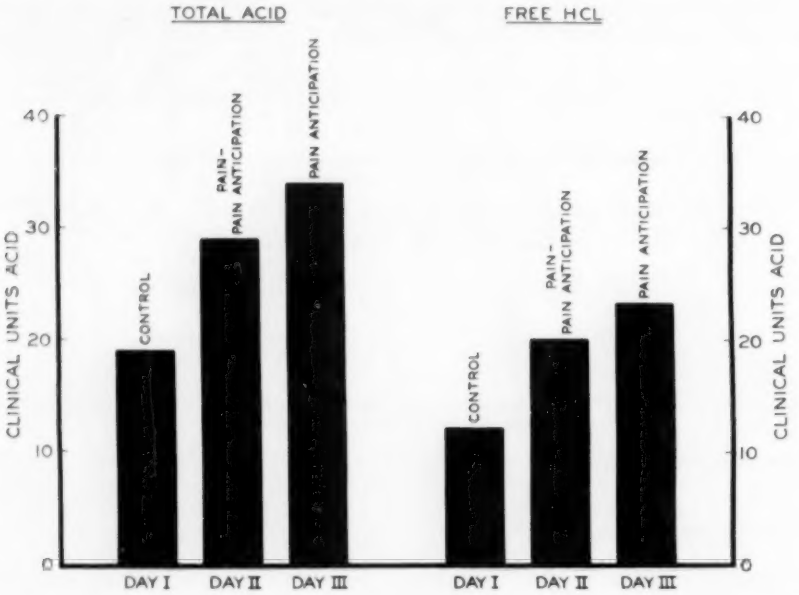

Chart 1.—Mean gastric acidity of 13 subjects during control, pain-pain anticipation, and pain anticipation conditions.

the pain anticipation condition of Day III is significantly higher than that during the control condition of Day I. The difference between Days II and III is not significant.

The mean gastric acidities of the "clearing" samples for these days are also presented in Table 2. There is no significant change in these. Furthermore, the net comparisons of the Day III-I test-sample differences with the Day III-I clearing-sample differences show that the increased gastric acidity of Day III was not due to day-to-day variability but was associated with the experimental stimulation of Day III. Since this net comparison of Day III-I differences brackets Day II, it is inferred that the Day II-I test sample changes are likewise not due to day-to-day variability. An inference is required here because the net comparison of the

TABLE 3.—*Mean Gastric Acidity in Clinical Units of Control and Experimental Groups*

		Control Group		Experimental Group		Reliability of Difference Between Means†
		$\bar{x}$	s	$\bar{x}$	s	
Total sample*	Total acid	25	12.3	37	17.4	$P = 0.10$
	Free HCl	16	11.5	27	19	$P = 0.13$
Restricted sample*	Total acid	21	8.8	39	18.2	$P = 0.04$
	Free HCl	12	7.4	29	19.9	$P = 0.06$

* "Total sample" includes all subjects assigned to the control and experimental groups prior to their participation as subjects. "Restricted sample" excludes from the control group the subject who sought but interrupted psychiatric treatment prior to this study and excludes from the experimental group the subject who felt the need for treatment but was not at the present time in treatment.

† Differences in variability were tested by the F test. None of the variability comparisons were significant at the 5% level.

Significance of differences between means was tested by the t test. P values are for the predicted difference between the control and the experimental groups.

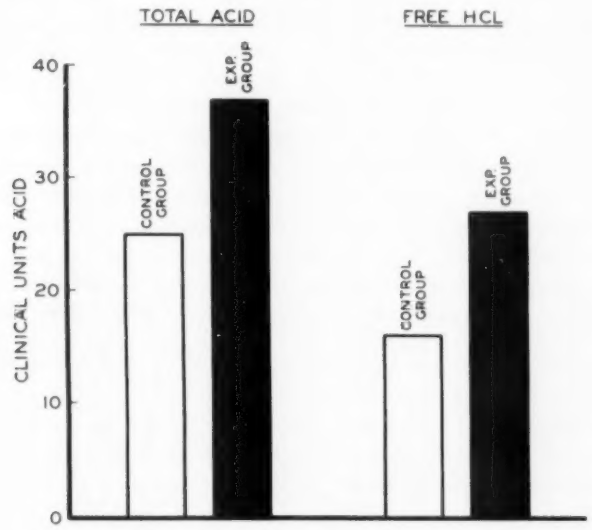

Chart 2.—Mean gastric acidity of control and experimental groups.

Day II-I test- and clearing-sample differences is unwarranted, since it involves "clearing samples" of Day II that were obtained after the pain-adjustment series, rather than after a five-minute rest period, as on Days I and III.

(*c*) Comparison of Gastric Acidity of Control and Experimental Groups: The mean acidity of the experimental group was higher on all three days than that of the control group. Since no differential secretory response on Days II and III was found between the two groups, the test measures on all three days were pooled for each group to test the significance of the difference between the groups as such. These pooled data are summarized in Table 3 and Chart 2.

Two summaries are contained in Table 3. The first compares all of the subjects as originally assigned to the control or the experimental group. The Table shows that the mean total acidity and free HCl of the experimental subjects are greater than those of the control subjects. The reliabilities of these differences are only fair.

The second summary of Table 3 compares the two groups when the subject who was not undergoing psychiatric treatment is omitted from the experimental group and the subject who had started but not continued with psychiatric treatment two years previously is omitted from the control group. The reliability of the differences in gastric acidity between these "restricted" groups is greater than that of the differences of the original control and experimental groups. A possible interpretation of these increases in reliability is presented in the discussion.

The groups were combined and then split at the median age into a "young" and an "old" group to determine the effect of age in the results. If the difference in gastric acidity between the control and the experimental groups is due to the age difference between them, then the "old" group should show a significantly higher acidity than the "young" group because the mean age for the experimental group was higher than that for the control group. There was no significant difference (t-test) in the gastric acidity of the two age groups ($P > 0.50$).

The results were also examined to see whether gastric acidity was related to the pain intensity measured in physical units and whether this relationship contaminated the control-experimental group acidity differences.

The mean response thresholds for the control and the experimental groups were determined. These were 307 and 284 mcal. for the original control and experimental groups, respectively, and 313 and 290 mcal. for the "restricted" control and experimental groups, respectively. Neither difference in the mean response thresholds is statistically significant ($P > 0.20$).

In addition, the distribution of response threshold intensities of all subjects was split at the median of 295 mcal. (range, 250-380 mcal.) and the mean secretory responses on Day II of the resulting low- and high-pain intensity groups were determined. The mean total and free-acid responses of + 10.9 and + 8.9 clinical units for the low-intensity group are practically the same as the mean total and free-acid responses of + 9.1 and + 8.7 clinical units for the high-intensity group. Thus, there was no relationship, over the range of intensities used here, between HCl secretion and the physical intensity of heat.

COMMENT

This study failed to contribute to the primary problem of determining whether there is a change from inhibited to increased HCl secretion in humans associated with the change from acute to sustained anxiety. Both groups presented sustained anxiety at the onset of the pain-pain-anticipation stimulation. This consisted of anticipatory anxiety evoked by foreknowledge of the experiment, which anxiety was not successfully reduced by reassurance and explanation, and chronic psychopathological anxiety in the experimental group. The result was a failure to achieve (in the control group) a condition of no, or very slight, pretest anxiety to change experimentally into acute-emergency anxiety. Verification of the acute-chronic anxiety hypothesis in humans remains an experimental problem. It will require fairly complete control of the pretest anxiety.

The difference in gastric acidity between the original "chronic anxiety" group and the control groups was of only suggestive reliability (total acid, $P = 0.10$). Two factors might be regarded as yielding an attenuated group difference in gastric acidity. First, the anxiety evoked by the prospect and actual occurrence of intuba-

tion seemed greater in the controls than in the experimental subjects. It may be that the latter more readily accept an uncomfortable medical procedure perceived as related to their medical study and treatment than the controls, who could only regard intubation as an experimental procedure.

A second attenuating factor may have been a function of variability in anxiety intensities among the individuals within each of the groups. It will be recalled that the experimental group included six psychiatric patients, five of whom were inpatients, and one person who was not a patient but who expressed the need for treatment and who was judged as presenting chronic anxiety symptoms. The possibility raised is not whether or not this person suffered from chronic anxiety, but that including her in this group increased considerably the range of the anxiety intensities represented by the members of the group. A comparable situation seems possible regarding the member assigned to the control group, who had sought, started, and then interrupted psychiatric treatment two years prior to this study. If one assumes that including these two subjects in the groups did have this effect, then eliminating them would increase the difference between the groups in the severity of chronic anxiety. If HCl secretion varies with chronic anxiety, the difference in gastric acidity between these more restricted groups should be greater and the reliability of this difference would be expected to increase. These two expectations were confirmed.

The HCl secretion of the subjects taken as a single group increased significantly upon both pain-pain anticipation and only pain anticipation stimulation. For the reasons stated earlier, the increased HCl secretion on Days II and III could not be predicted. It can be explained by alternative proposals. One is that the interaction between the pretest and the experimental anxiety was cumulative and that the rise in HCl secretion was associated with this increase in anxiety. Another proposal is that such a functional change in the autonomic innervation pattern results from sustained anxiety reactions that any subsequent discrete anxiety stimulus evokes increased HCl secretion. This latter proposal does not concern itself with the interaction between the pretest and the experimental anxiety reactions. The main value of this result is the empirical finding of increased HCl secretion in humans related to a specifiable stimulus that interacts with sustained anxiety.

The condition of pain anticipation (Day III) was just as effective in evoking increased HCl secretion as the condition of pain and pain anticipation (Day II). A similar finding was obtained with dogs and monkeys. These observations demonstrate that increased HCl secretion is part of [5] acquired anxiety reactions (preceded by or evoked during sustained anxiety) that are produced by experimental procedures in dogs, monkeys, and humans. The difference in the gastric acidity of the two groups in this study—the increased gastric acidity in students reacting with "examination anxiety" and the increase in HCl during anxiety-laden psychoanalytic hours in a chronically anxious patient—demonstrates that increased HCl secretion is part of sustained acquired anxiety reactions produced by "real-life" procedures. Studies by others cited in the introduction yielded compatible results.

The consistent finding of increased HCl secretion during acquired anxiety reinforces the belief that the role of chronic anxiety in peptic ulcer etiology requires detailed investigation.

SUMMARY

The evidence that increased HCl secretion occurs during sustained anxiety is contradictory to the unqualified extension of the emergency theory of emotions to chronic emotions. Results of studies with dogs and monkeys indicate that this increased HCl secretion is a function of the change from acute-emergency to sustained anxiety. The problem of the present experiment was to test this conclusion in humans and to obtain further empirical data of HCl secretion and anxiety in humans.

The procedure consisted of (*a*) comparing the fasting gastric acidity levels of seven subjects presenting chronic anxiety symptoms and of a group of seven subjects not presenting such symptoms; and (*b*) comparing the fasting HCl secretory response of these two groups when subjected to one experimental anxiety-evoking situation based upon pain and pain anticipation stimulation and another consisting only of pain anticipation stimulation.

Because of methodological limitations, the desired differential pretest anxiety in the two groups was not obtained. Therefore the nature of HCl secretion during acute-emergency anxiety could not be studied.

The gastric acidity of the original "chronic anxiety" group was greater than that of the control group, but this difference was of only suggestive reliability. When one subject was eliminated from each of these groups on specified grounds in order to make the groups more homogeneous in anxiety, the gastric acidity of the "chronic anxiety" group was significantly greater than that of the control group. When pain and pain-anticipation stimulation and response interacts with the sustained pretest anxiety, there is a significant increase in HCl secretion.

Both these findings are consistent with previous studies of sustained anxiety and HCl secretion. The accumulated evidence (*a*) reveals the invalidity of the unqualified extension of the emergency theory to the chronic emotions involved in psychosomatic disorders and (*b*) reinforces the belief that the role of chronic anxiety in peptic ulcer etiology merits detailed investigation.

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BILATERAL INTRACRANIAL ANEURYSMS

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THE FIRST English record of an intracranial aneurysm was reported by Sir Gilbert Blane [2] in 1800. In this historic case the autopsy was done by Hunter and Holme and was witnessed by Blane and Jenner. Bilateral aneurysms were found.

Subsequent to this, reports of bilateral intracranial aneurysms found at autopsy or operation have appeared sporadically in the literature: Bourneville [3] (1868) reported 1 case; Bartholow [1] (1872), 8 cases; Pitt [13] (1890), 2 cases; Fearnsides and Cantab [7] (1916), 3 cases; Conway [5] (1926), 1 case; Shore [16] (1928), 1 case; Schmidt [17] (1930), 2 cases; Magner [12] (1935), 1 case; Bozzoli [4] (1937), 1 case; McDonald and Korb [11] (1939), 9 cases; Hamby [8] (1942), 1 case; Riggs* (1943, 1952), 13 cases, and Poppen [14] (1951), 3 cases.

With improvement in techniques of visualization of intracranial arteries and more frequent surgical intervention in cases of aneurysm, it was felt worth while to review the cases of suspected intracranial aneurysms at the University of Pennsylvania Hospital in order to define a more definite approach to this problem.

This paper is based upon a series of 162 angiograms obtained from 1940 through 1952 on 121 patients suspected of having an intracranial aneurysm (Table 1).

Of the 121 aneurysm suspects, 34 had bilateral carotid angiograms, and 5 of these had vertebral angiograms. Of these 34, aneurysms were demonstrated in 18; being unilateral in 12 (66.6%) and bilateral in 6 (33.3%). In 16 an aneurysm was not found (Table 2). An aneurysm was demonstrated in 39 of the 87 unilateral carotid visualizations, and no aneurysm was found in 48 (Table 3). One patient of each group had an additional vertebral angiogram. In reviewing the histories of the entire group, it was felt that signs pointed to the vertebral-basilar circulation in 12 cases in which vertebral angiography was not done.

The diagnosis of aneurysm was confirmed in 57 of these 121 cases, or in 47.1%. However, positive confirmation in patients with subarachnoid hemorrhage was

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* Reference 15. Personal communication to the authors.

higher than in those with localizing signs without evidence of hemorrhage (Table 4); that is, in 39 of 70 patients with hemorrhage (56.7%) and in 18 of 51 without hemorrhage (35.0%).

TABLE 1.—*Angiographic Findings in 121 Patients with Intracranial Aneurysm*

	No. of Patients	No. of Carotid Angiograms	No. of Vertebral Angiograms	Total
Unilateral angiography in aneurysm suspects..	87	87	2	89
Bilateral angiography in aneurysm suspects....	34	68	5	73
Vascular anomaly suspects.....	21	28	1	29
Other lesions suspected, chiefly tumors.....	192	208	4	212
Totals.....	334	391	12	403

TABLE 2.—*Bilateral Angiograms in Aneurysm Suspects*

	No.
No. with unilateral aneurysm.....	12
No. with bilateral aneurysm.....	6
No. in whom no aneurysm demonstrated.....	16
Total with bilateral angiograms.....	34

TABLE 3.—*Unilateral Angiograms in Aneurysm Suspects*

	No.
Aneurysm demonstrated	39
Aneurysm not demonstrated.....	48
Total with unilateral angiograms.....	87

TABLE 4.—*Incidence of Aneurysm in Patients With and Without Subarachnoid Hemorrhage*

	Bilateral Aneurysms	Unilateral Aneurysms	No Aneurysm Found
Subarachnoid Hemorrhage			
1. Bilateral angiogram	6	11	10
2. Bilateral and vertebral angiogram.....	..	1	4
3. Unilateral angiogram	..	21	16
4. Unilateral and vertebral angiogram.....	..	..	1
Suspected Because of Localizing Signs			
1. Bilateral angiogram	..	..	2
2. Bilateral and vertebral angiogram.....	..	..	..
3. Unilateral angiogram	..	17	31
4. Unilateral and vertebral angiogram.....	..	1	..
Totals.....	6	51	64

It should be noted that in making this review an additional 21 patients were demonstrated to have vascular anomalies, such as angiomata or arteriovenous malformations. In this group confirmation of the diagnosis was 90%. Additional evidence, such as vascular lesions of the face, focal seizures, bruits, calcifications or increased vascular markings on plain skull films, and increased cerebral blood flow, contributed to the high percentage of confirmati- ns.

REPORT OF CASES

The following are the case histories on the six patients with bilateral aneurysm as shown by angiography with an additional case verified at autopsy.

CASE 1.—J. J. M., a 52-year-old white man, was admitted to the hospital Oct. 9, 1950, three months after the first episode of subarachnoid hemorrhage. There was a history of sudden pain above the right eye with nausea, profuse perspiration, and subsequent coma. Severe frontal headache and stiff neck developed. Bloody spinal fluid was found on examination at the referring hospital.

On admission he showed some memory impairment for events of the present illness but no localizing neurological signs.

Routine skull films were negative. Spinal fluid pressure was 120 mm. of water with 6 W.B.C. per cubic millimeter and normal protein.

A right carotid angiogram done Oct. 14 showed a large aneurysm of the right carotid artery at its junction with the posterior communicating artery (Fig. 1*A*).

The patient did not wish surgery and was allowed to go home, to be followed closely by his local physician.

He did well until Nov. 11, 1950, at which time he told his wife there was something wrong with his head, sat down, and had a generalized seizure. He was readmitted to the hospital Jan. 1, 1951, where a second subarachnoid hemorrhage was confirmed. His only complaint was headache involving the left frontal region.

Physical examination showed him to be mentally depressed, oriented, but very dependent upon his family. His affect was very labile. There was slight drifting downward of the right arm when held at shoulder level, and he had generalized weakness with no definite inequality; the left pupil was slightly larger than the right.

A left carotid angiogram revealed an aneurysm in the same position as that on the right (Fig. 1*B*). Clipping of both aneurysms was discussed, but his family did not wish surgery and he was discharged Jan. 11, 1951, on anticonvulsant therapy.

He expired at home Feb. 11, 1951, as a result of recurrent hemorrhage. Autopsy was not performed.

CASE 2.—E. H., a 22-year-old white man, was first admitted to the hospital Sept. 16, 1948, for investigation of a suspected vascular anomaly. He had the onset of seizures at the age of 12 years. These were infrequent and usually nocturnal. Epilepsy was diagnosed while he was in the Navy in 1944, after a seizure. The last seizure occurred three years prior to admission, when he remained conscious and had clonic movements of the head. The patient had a family history of seizures (a cousin).

One and a half months prior to admission, while playing baseball, he felt dizzy. He then became unconscious for a short while, awaking with a severe generalized headache and vomiting. Four days later evidence of subarachnoid hemorrhage was found—bloody spinal fluid, which gradually cleared, as did the headache and blurred vision.

After discharge from the local hospital he felt tired out but had no other symptoms until Sept. 9, 1948, when he experienced a "pressure in the head" on attempting to lift a heavy object. He was then admitted to the Hospital of the University of Pennsylvania, where plain skull films revealed a cluster of calcifications fairly close to the midline in the right frontotemporal region.

Right carotid angiography revealed an arteriovenous malformation in the frontalparietal region, with two aneurysmal dilatations (Fig. 2*A*). He was discharged on anticonvulsant therapy.

He was readmitted March 27, 1952, having had increased irritability for three to four months, with nausea and headache following a "snap in the back of the head" 12 days prior to admission. On the day of readmission he had sudden severe head pain, which caused him to sink to his knees. When he was helped to a couch, he was noted to have weakness of the right side of his body. He became disoriented and semistuporous, but by the time of admission (four to five hours later) he was again able to move the right side.

Examination showed the patient to be semistuporous. He was able to move all extremities, but strength could not be tested. There was slight right facial weakness. The deep reflexes

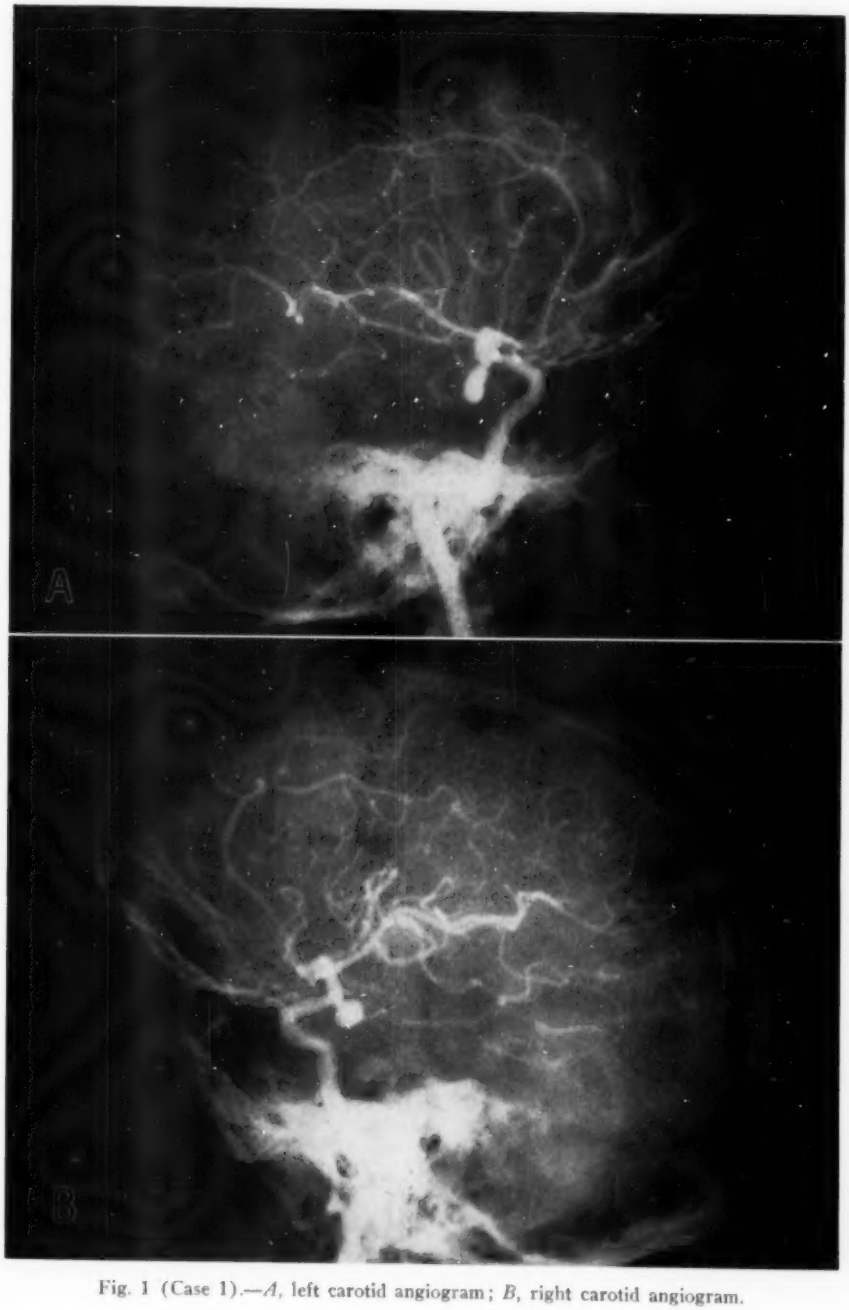

Fig. 1 (Case 1).—*A*, left carotid angiogram; *B*, right carotid angiogram.

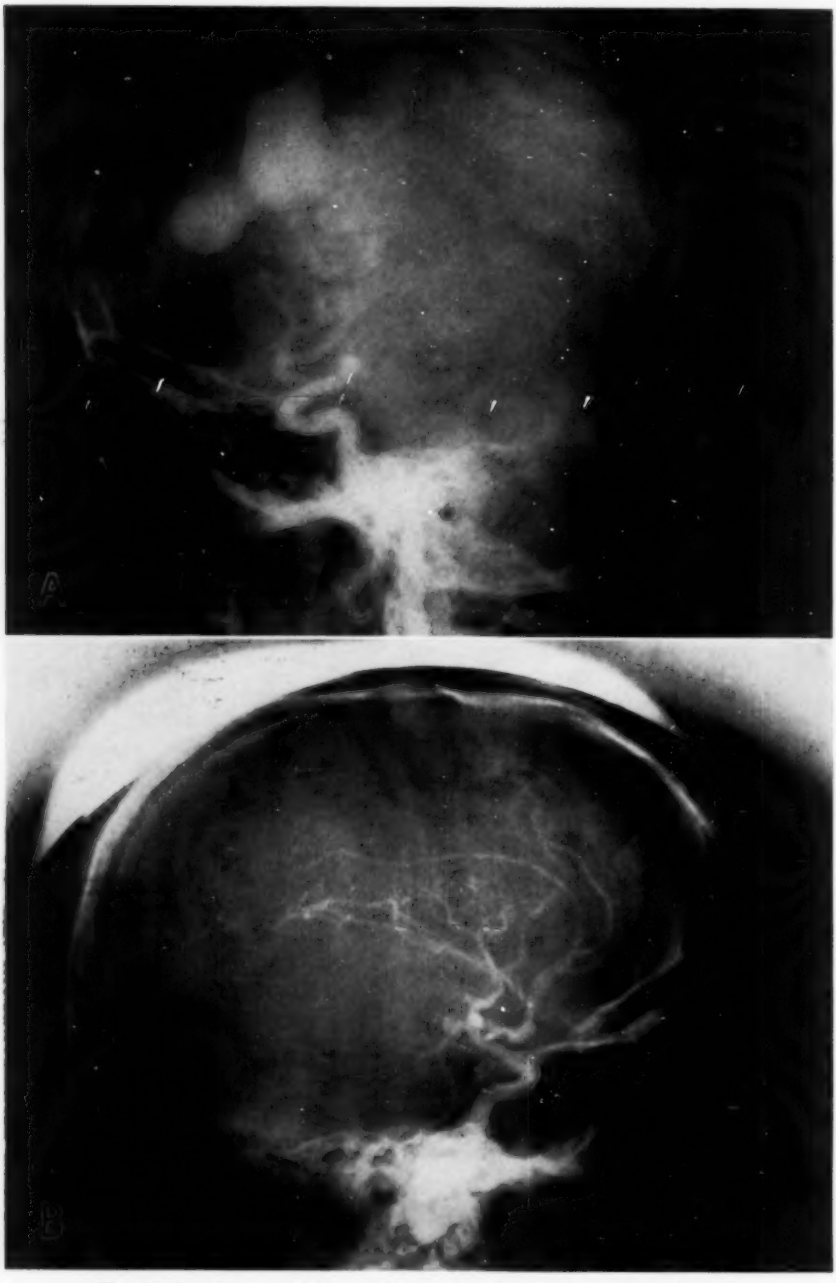

Fig. 2 (Case 2).—*A*, right carotid angiogram; *B*, left carotid angiogram.

were absent except for the Achilles reflexes, which were equal. Abdominal reflexes were decreased on the left and were not obtained on the right. There was an equivocal Babinski sign bilaterally. Sensation and cranial nerves were intact.

Lumbar puncture revealed a pressure of 270 mm. of water, grossly bloody fluid, but with a xanthochromic supernatant, and protein of 398 mg. per 100 cc.

A left carotid angiogram was performed April 7, 1952, which revealed two aneurysms, one from the site of origin of the posterior cerebral artery and the second from the proximal portion of the anterior cerebral artery near the midline (Fig. 2*B*). The headache subsided considerably; the spinal fluid pressure fell, but the fluid was still xanthochromic when he was discharged, April 12, 1952, to continue bed rest at home. Surgical intervention was not considered wise.

He has been followed in the Outpatient department but has been unable to do any sort of work; he cannot even play games with his children because of headaches and dizziness. However, at the time of his last visit the neurological examination was negative.

Case 3.—N. A., a 46-year-old Negro woman, was admitted to the Hospital of the University of Pennsylvania Oct. 29, 1949. She had a history of three episodes of spontaneous subarachnoid hemorrhage within one year (Nov. 6, 1948; Feb. 5, 1949, and Sept. 20, 1949), all of which were confirmed by spinal fluid examination and responded to conservative therapy. There had been no localizing signs at any time. She was found to have syphilis in 1948 and had received penicillin therapy.

Physical examination was normal except for early Grade II arteriosclerotic retinopathy. The neurological examination was normal.

Spinal fluid examination showed a pressure of 180 mm. of water. The fluid was clear and colorless, with five white cells per cubic millimeter, 38 mg. protein per 100 cc., a negative Kolmer reaction, and a colloidal mastic curve of 1222210000.

Plain skull films were negative. Bilateral carotid angiography revealed bilateral aneurysms. On the left there were two aneurysms, one at the origin of the posterior communicating artery, the other, larger, aneurysm on the left middle cerebral (Fig. 3*A*). On the right there was one, and possibly two, aneurysms of the middle cerebral artery near its origin (Fig. 3*B*).

Surgery was not thought feasible, and she was discharged with instructions to avoid strenuous exercise.

She was admitted to a local hospital Jan. 7, 1951, with evidence of recurrent hemorrhage. She expired Jan. 25, 1951.

Case 4.—E. A., a 31-year-old Negro woman, was admitted to the hospital April 12, 1952, after a sudden loss of consciousness and generalized seizure. On regaining consciousness she had difficulty in speaking. Her left leg was numb and weak, but this and the speech disturbance cleared within a few minutes. She had a severe generalized headache with vomiting.

Daily occipital headaches had afflicted her for two years. Her mother died at the age of 42 years of an "aneurysm in her head."

On admission, examination revealed blood pressure 90/60, pulse 80, respiration 20, decreased left hand grip, left biceps reflex more active than the right, stiff neck, and preretinal hemorrhage O.D.

Lumbar puncture revealed bloody cerebrospinal fluid under 95 mm. of water pressure.

She was treated conservatively. Her last lumbar puncture, which was done April 19, 1952, showed clear, colorless fluid under normal pressure.

Plain skull films were negative.

A right cerebral angiogram was done May 19, 1952, and showed an aneurysm springing from the internal carotid artery just proximal to the bifurcation. A left angiogram was attempted May 27, 1952, but was unsuccessful.

She was discharged May 28, 1952, to be readmitted for left carotid angiography.

She was readmitted Aug. 20, 1952, still complaining of intermittent headaches. Left carotid angiography, done Aug. 21, revealed an aneurysm springing from the bifurcation of the left internal carotid artery.

Surgery was not felt advisable, and she was discharged, to be followed in the clinic.

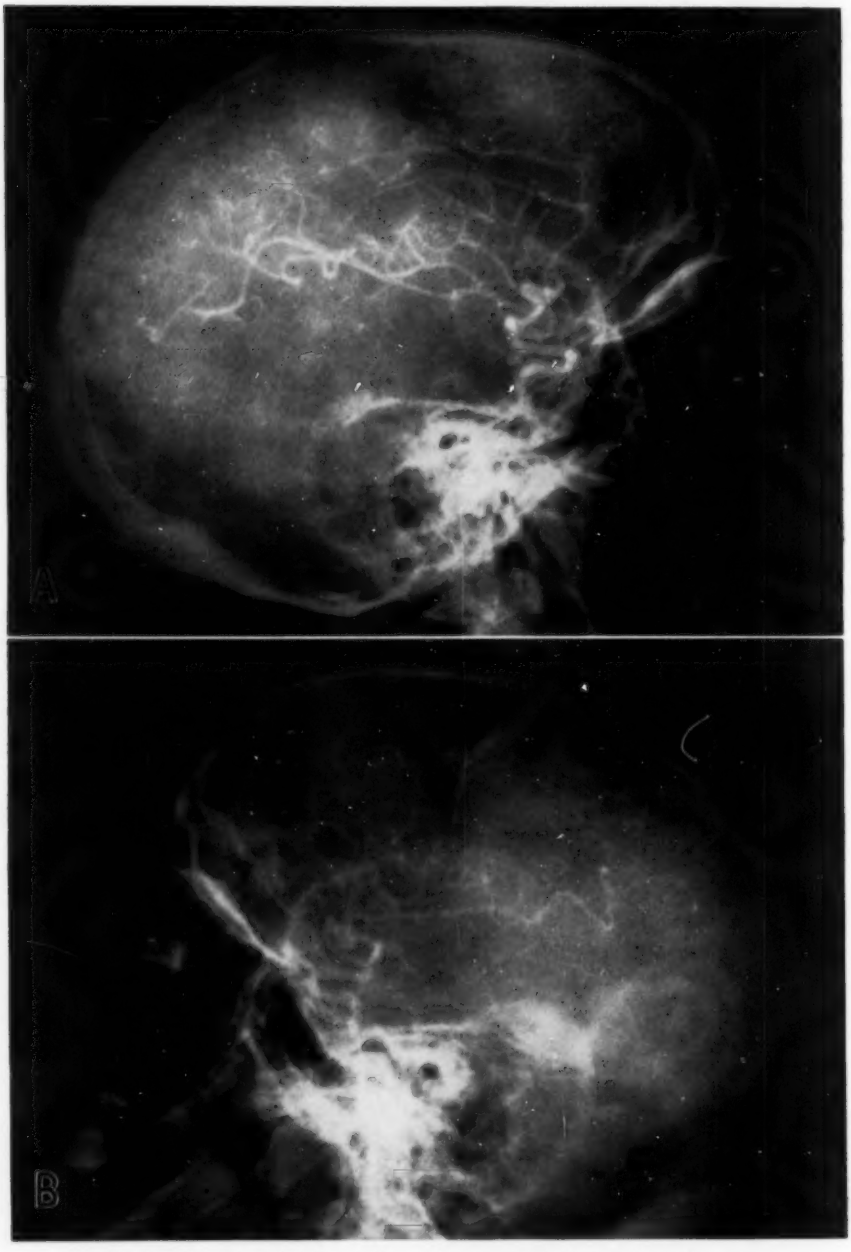

Fig. 3 (Case 3).—*A*, left carotid angiogram; *B*, right carotid angiogram.

CASE 5.—M. T. J., a 34-year-old housewife, was transferred April 27, 1952, from a local hospital, where the diagnosis of subarachnoid hemorrhage had been confirmed by lumbar puncture.

There was a history for several years of "migraine headaches" involving the entire head and accompanied by vomiting.

On April 16, 1952, she developed frontal headache, vomited, and gradually, over a two- to three-hour period, became comatose. She was treated with bed rest and frequent lumbar punctures. The patient was six weeks postpartum at the time of her illness.

On admission to the Hospital of the University of Pennsylvania, she was semistuporous, disoriented, and unable to follow instructions. There was slight left hyperreflexia with a positive Babinski sign on the right. There was impairment of extraocular movements, but the examiner was unable to determine which muscles were weak. There was bilateral blurring of the optic disc.

Spinal fluid pressure was 310 mm. of water, and the fluid was xanthochromic.

Ophthalmological consultation on the second day showed blurring of the discs and what was thought to be paresis of conjugate gaze to the left.

She was mentally obtunded and disoriented for several weeks. Her eyes were rechecked frequently, with no evidence of ocular palsy after the initial examinations. By May 26 enough cooperation was obtained to demonstrate a right homonymous hemianopsia. This had become a right homonymous inferior quadrantanopsia, which was congruous before discharge, and the papilledema had subsided. She complained of pain of a rather vague character in the right hip and thigh prior to discharge.

Bilateral carotid angiography was performed. The right angiogram showed slight spasm of the proximal portion of the anterior cerebral artery and a questionable aneurysmal lesion in the carotid siphon. The left showed a small berry aneurysm springing from the internal carotid artery just above the site of origin in the ophthalmic artery.

It was the opinion of the neurological and neurosurgical departments that rupture of the aneurysms demonstrated by angiography could not explain the findings and that she probably had additional aneurysms.

When last seen, April 8, 1953, she complained only of pain in her right thigh and leg and had a decreased Achilles reflex on the right.

CASE 6.—P. K., a 43-year-old white man, was admitted to the Hospital on Jan. 31, 1950. He had a history of sneezing Jan. 12, 1950, following which there was a "snap" in the back of his head. He then experienced temporary blindness and complained of severe headache and stiffness in his neck. Eighteen hours later he was found unconscious on his bathroom floor. He was admitted to the referring hospital, where lumbar puncture showed grossly bloody cerebrospinal fluid. He gradually improved but remained dull and confused.

When lumbar puncture was done Jan. 25, the initial pressure was 270 mm. of water, with xanthochromic fluid.

On his admission to the Hospital of the University of Pennsylvania, his blood pressure was 120/80 and his general physical examination was normal. He was rational and oriented but somewhat vague and quiet. The neurological examination was normal, including the fundi and visual fields.

X-rays of the skull were normal except that the right orbit appeared denser than the left.

Bilateral carotid angiography was performed Feb. 6, 1950; that on the left side was repeated Feb. 14. An aneurysm was seen in the left parasellar region and an aneurysm in the same region on the right.

He was allowed to return home and resume work after a two- to three-week period of rest.

When last seen, Jan. 10, 1951, he was symptom-free with no abnormal neurological findings.

CASE 7.—K. B., a 27-year-old white man, was admitted to the general surgery service Jan. 2, 1952, for correction of coarctation of the aorta. He had been discharged from military service in 1943 because of hypertension. He had always had some weakness of the lower extremities, and his feet were always cold. For approximately 10 years he had had frequent episodes of epigastric pain, relieved by food. Five weeks prior to admission he had the onset of episodes characterized by an odor of "natural gas in the back of his nose," accompanied by

generalized weakness or tiredness and perspiration, lasting for 10 to 15 seconds. The second episode occurred three weeks after the first, and these episodes recurred two to three times daily thereafter.

Physical examination revealed blood pressure of 220/120 in the arms; not obtainable in the legs. Pulsations were poor in the lower extremities; there was evidence of collateral circulation with visible and pulsatile vessels over the scapular area. The heart was slightly enlarged to the left with a precordial bruit of late systolic time; there were no congestive signs. There was Grade II hypertensive retinopathy but no abnormal neurological findings, including visual fields.

Routine blood and urine studies were normal. An x-ray of the chest showed notching of the ribs and hypoplasia of the aortic bulb. An angiocardiogram revealed a fairly long narrowed segment in the descending portion of the aortic arch. The skull x-ray was normal. Spinal fluid examination was normal.

The electroencephalogram showed a few sharp waves in the left temporal area.

It was felt that the presence of a vascular anomaly, i. e., an aneurysm, was the most likely cause of the uncinate fits. Cerebral angiography was not done to confirm this, since it was believed that decreasing the cerebral blood pressure by repair of the coarctation would reduce the possibility of rupture.

Operation was performed on Jan. 9, 1952, when the coarctation was replaced by an arterial graft. He did well after operation except for some pain in the epigastrium and the left upper quadrant, which was present after the second day. His blood pressure was reduced from 220 to 150 systolic in the arms.

On the 14th postoperative day he developed a sudden severe headache with pallor and profuse perspiration. The blood pressure was found to be 240/120. About 10 minutes later he again complained of headache and became unresponsive, with extensor spasm and stertorous respirations. A lumbar puncture showed grossly bloody cerebrospinal fluid under a pressure of 450 mm. of water. There were no localizing neurological signs, and surgical intervention was not felt possible. He expired within six hours of the onset of the bleeding.

Postmortem examination of the brain revealed aneurysms on both middle cerebral arteries with rupture of the aneurysm on the right into the right temporal lobe, the subarachnoid space, and the right temporal horn of the ventricular system.

COMMENT

The primary purpose of this paper is to call attention to the frequency with which bilateral intracranial aneurysms occur and to point out the influence thereof upon therapeutic management. It is often possible on clinical grounds to suspect an aneurysm and to determine the side of the lesion. Too often, however, if a carotid angiogram confirms this impression, ligation or other surgical intervention is performed without examining the vessels of the other side. That the problem is not one of academic interest, but one of a very practical nature, has previously been illustrated by Poppen.[14] He reported deaths following ligation for a visualized aneurysm in three cases proved by autopsy to have bilateral aneurysms, with several others in which this situation was strongly suspected but autopsy was not permitted. We believe, as does Poppen, that the internal carotid circulation of the opposite side should be investigated before a surgical procedure is instituted for a demonstrated aneurysm. An exception to this rule, of course, would have to be made if immediate surgery were indicated as a lifesaving measure.

In our small group in which bilateral angiography was done there were 33% with bilateral aneurysms. This is much higher than was indicated by a review of previous reports, there being only 0.87% of bilateral aneurysms in McDonald and Korb's[11] series (9 cases with bilateral aneurysm in 1,023 cases in which the artery involved was known). Hamby[9] reported a series of 94 aneurysms in 86 patients,

4, or 4.6%, having bilateral aneurysms. However, all of this series did not have examination of both carotid arteries, either by direct examination or angiographically.

The posterior (vertebral-basilar) circulation is no longer considered inaccessible surgically, and vertebral angiography should be done oftener. We are not, however, advocating vertebral angiography in all cases of suspected aneurysm, because the incidence is only 14%. It is indicated when symptoms point strongly to this region and when the lesion is not found with bilateral carotid angiography. In short, there seems to be no serious consideration of excluding a vertebral aneurysm when a unilateral aneurysm is demonstrated.

We have found only three such instances reported. Hamby [9] reported a case with an aneurysm on the right middle cerebral artery and a second on the bifurcation of the basilar. McCordock [10] reported a case of an aneurysm on the right posterior communicating artery, one on the basilar and a third on the left internal carotid. Ruston and Southard [16] reported a case of bilateral vertebral and miliary cerebral aneurysms.

One of our series showed an aneurysm of the left posterior cerebral artery and one at the bifurcation of the left internal carotid artery. Another showed an aneurysm at the junction of the right posterior cerebral and the posterior communicating artery.

SUMMARY

A series of 121 patients suspected of having an intracranial aneurysm, and on whom carotid angiography was performed, is reviewed.

A higher incidence of bilateral lesions in those having bilateral visualization was found than has previously been reported—6 of 18, or 33.3%.

The incidence of confirmation of an aneurysm was higher in patients having subarachnoid hemorrhage than in those having localizing signs without subarachnoid bleeding—56.7 and 35%, respectively, while confirmation of vascular anomalies was 90%.

Emphasis is placed upon the need for bilateral carotid visualization before surgery is instituted, and more frequent vertebral angiography is advocated.

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COGAN'S SYNDROME

(Nonsyphilitic Interstitial Keratitis with Deafness)

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THE COGAN syndrome is characterized by sudden onset of photophobia, ocular pain, blurring of vision, and blepharospasm. Usually, within a few hours to a few weeks evidence of eighth nerve involvement appears, manifested by tinnitus, nausea, vomiting, vertigo, and bilateral progressive loss of hearing. The vestibular symptoms are almost identical with those found in Ménière's syndrome, may precede the ocular manifestations, and usually resolve when the deafness is complete. The evolution of the complete syndrome is usually rapid. Interstitial keratitis appears early. It is always bilateral, fluctuates in its severity, and is not associated with retinal disease. Visual acuity diminishes and vascularization of the cornea finally eventuates. Serological and clinical evidence of syphilis is consistently lacking.

The disease is considered rare, with the usual implied qualification that many instances are missed or incorrectly diagnosed. Cogan in his original account in 1945,[1] collected four cases in one year and subsequently reported four more in 1949.[2] However, to date only 16 cases have been described.[3]

The following case typifies this syndrome except that this is the first instance of it in a child.

REPORT OF A CASE

M. W., a 10-year-old girl, had been under close medical surveillance at Group Health Clinic since birth. Development was normal, and the usual childhood diseases that she suffered were not associated with any unusual sequelae. At the age of 4½, a tonsillectomy was followed by postoperative hemorrhage, which was controlled in the usual way without any complications. About one month after this there was generalized lymphadenopathy with slight fever, associated with a sore throat. The spleen was not palpable, and the heart was normal. Three months later the first symptoms involving the eyes appeared and were characterized by bilateral injection of the conjunctiva and epiphora. Over the next three months, she had frequent sore throat, her eyes remained injected, and tearing became profuse. The lymphadenopathy cleared completely. Tripelennamine hydrochloride (Pyribenzamine) was administered in the hope that the ocular signs would be improved, but this was ineffectual. Ophthalmologic consultation was sought, and at that time impaired acuity was noted. The right eye showed 20/150 vision and the left eye 20/200 vision. The corneas were edematous; photophobia was marked, and funduscopic examination was impossible. The eyes were examined under anesthesia, but details of the fundus could not be made out because of the cloudy cornea. Intraocular tension was normal. Lenses did not correct the decreased visual acuity. The ophthalmologic diagnosis at that time was congenital keratitis. Repeated examination showed considerable variation in the patient's acuity, and two years after onset vision in the right eye was 20/20 and in the left

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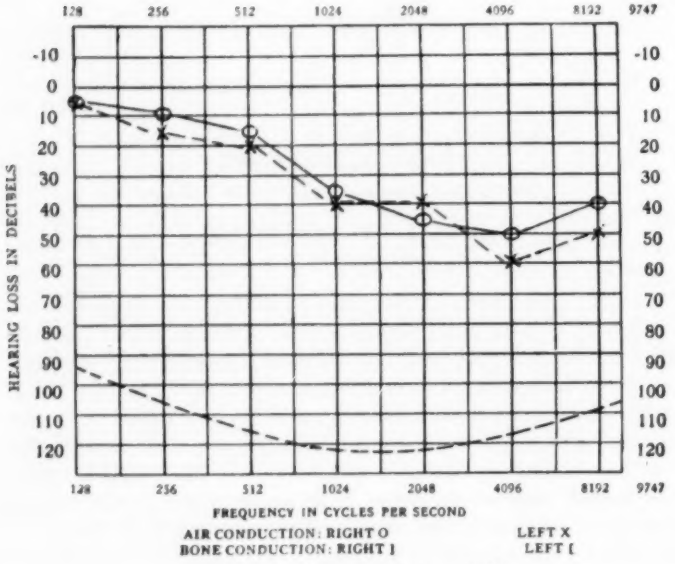

Fig. 1.—Audiogram in August, 1952.

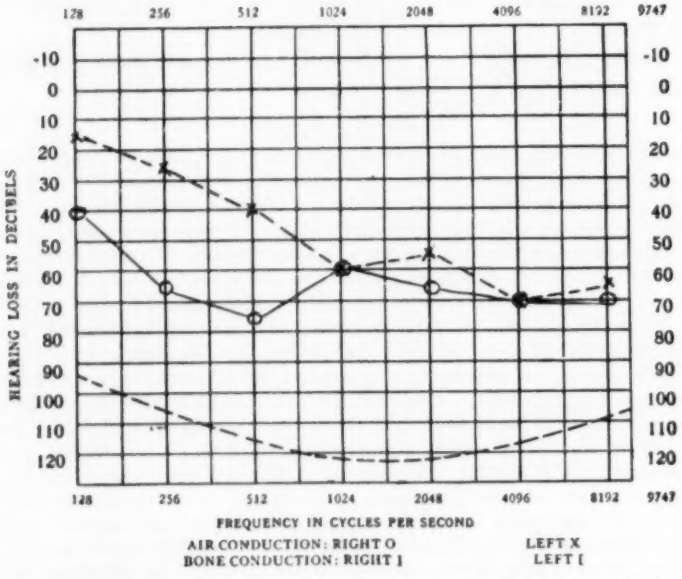

Fig. 2.—August, 1953, audiogram demonstrating hearing decrement in period of one year.

eye 20/100. Two years after onset of illness an attack of acute iritis appeared in the right eye and gradually disappeared. Photophobia and injection of the conjunctiva also improved. Cortisone (Cortone) drops six times a day were employed, but without noticeable effect.

About two years after the onset of the ocular symptoms, deafness was observed. An audiogram done in August, 1952, showed bilateral severe impairment of hearing (Fig. 1).

Fig. 3.—Patient at time of report.

Repeated audiograms indicated progression of the deafness, which involved first the higher tones but finally the entire range. Repeated otological examination revealed no further signs or defect, and it was the opinion of the otologist that this might represent congenital syphilis. Repeated physical examinations by the various pediatricians at Group Health Clinic revealed no other affliction, and the child continued to develop normally.

Blood Wassermann tests repeated three times were all negative. A spinal fluid examination in October, 1952, was completely negative. The child continued to run a constant eosinophilia,

the count ranging from 2 to 8%. In addition, there was a slight tendency to leucocytosis, the total count ranging from 10,000 to 12,700 per cubic millimeter, with a normal differential count. The rest of the hemogram was normal.

Because of the progressive deafness and impaired vision, the patient was referred for neurological consultation. This showed the following:

There were no stigmata of congenital syphilis; the facies were normal and alert, and mentality was above average. Station, gait, and coordination were intact. Muscle strength and tonus were equal and normal on the two sides. There was marked photophobia, and the cornea was too opaque to permit visualization of either fundus. The conjunctivae and upper lids were slightly injected. No granules were present under the lids. There was slight epiphora. There was no evidence of cataract or fibrous dysplasia. The pupils reacted to light and in accommodation, and extraocular movements were normal. Her voice seemed somewhat high-pitched and monotonous. Sensation was intact in all modalities. The deep reflexes showed absence of patellar reflexes, even with the reinforcement maneuver. There was no Babinski sign.

The neurological diagnosis was Cogan's syndrome, and it was recommended that the patient be given oral cortisone therapy after preliminary laboratory studies had been completed. Of these, a sedimentation rate was normal. X-rays of the hands and feet to exclude Boeck's

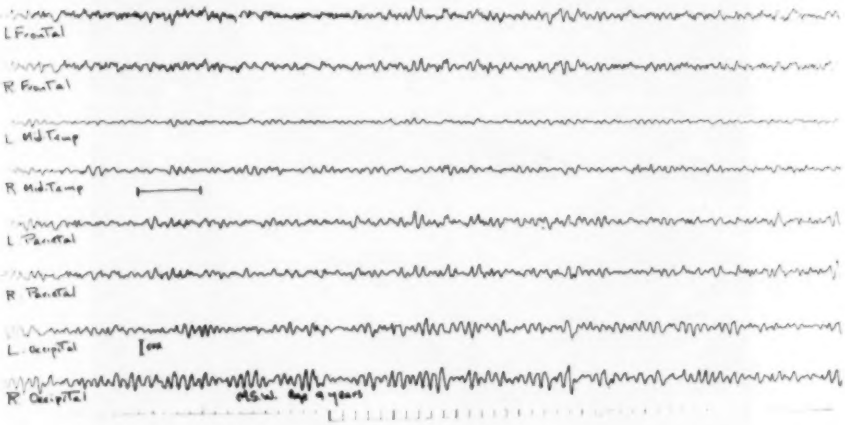

Fig. 4.—Electroencephalogram at age of 9 years.

sarcoid were normal. Chest and skull were roentgenologically normal also. Repeated blood counts continued to show eosinophilia, and a total eosinophile count ranged up to 500. Caloric tests were ordered, and the response was demonstrated to be completely absent in the right ear and normal in the left ear. Skin test, dye test, and complement fixation test were negative for toxoplasmosis.

Visual fields showed marked bilateral constriction, but their significance could not be appraised because of the patient's inability to cooperate, largely due to photophobia. Acuity in August, 1952, was 20/200 in the right eye and 20/100 in the left eye. When examined in August, 1953, the vision in the right eye was 20/200 and in the left eye 20/50.

A review of the family history indicated that the patient has three siblings, all in good health and none demonstrating any of the symptoms that the patient has. Blood and spinal fluid examinations on the parents were completely negative.

The patient was placed on cortisone therapy, starting with 100 mg. every six hours for the first day, 50 mg. every six hours for the second day, then 25 mg. q. i. d., and, finally 12.5 mg. a day. She was kept under observation daily by Dr. Ralph Stiller, and repeated blood pressures, weight, etc., were taken. A hearing aid was procured for the patient, which only partially improved her auditory perception. In spite of her handicaps, she is making a satisfactory social and scholastic adjustment, and at no time has there been any evidence of intellectual impairment. An electroencephalogram is completely normal (Fig. 4).

The above case demonstrates the classical pattern of Cogan's syndrome except for the age of the patient. Most cases occur in young adults.

The onset with epiphora, photophobia, blepharospasm progressing to impaired vision, and interstitial keratitis is typical. The associated progressive bilateral deafness, which as yet is not complete, is also characteristic. Improvement in hearing has been observed in 25% of cases,[3] although usually if deafness is complete it is permanent. Eighth nerve dysfunction sometimes precedes the ocular manifestations, as in the case of Grennan and Rones.*

No clinical or serological manifestation of syphilis could be found in the child or in the parents.

The eosinophilia and leucocytosis were mild, but consistent, and also frequently accompany this syndrome, the count usually ranging between 5 and 8%. However, Cogan reported a patient with a 28% eosinophile count.[2]

Characteristically, the spinal fluid was normal and the neurological examination showed only the interstitial keratitis and bilateral eighth nerve involvement. The electroencephalogram, as noted, was normal. Lindsay [4] also reported a normal electroencephalogram in one case, while Donald and Gardner [5] described a case in which the encephalogram showed "diffuse organic cerebral changes." Three generalized convulsions occurred in their patient.

The chief semiology may be condensed into the triad: (1) interstitial keratitis, (2) progressive bilateral deafness, and (3) negative serology.

In the differential diagnosis, syphilis deserves particular consideration. Interstitial keratitis and deafness individually and certainly coexisting, particularly in a child, suggests a syphilitic etiology. Stokes [6] says that deafness is present in 10% of patients with hereditary syphilis and found interstitial keratitis the commonest associated lesion. Interstitial keratitis is almost exclusively due to congenital syphilis and is present in about 80% of the cases. The interstitial keratitis in Cogan's syndrome differs from that in syphilis in that the severity varies, it is relatively mild, and there is absence of any intraocular disease.

In addition to syphilis, the symptoms of Cogan's syndrome suggest Ménière's syndrome, and in most of the cases in the literature the vestibuloauditory manifestations in the early course of Cogan's syndrome are indistinguishable from a typical Ménière syndrome. This includes progressive deafness, which, when complete, marks the termination of the episodes of vertigo, nausea, vomiting, loss of balance, etc. However, the bilaterality of the eighth nerve involvement and the coexisting ocular symptoms would militate against the diagnosis of Ménière's syndrome.

Also to be excluded is Heerfordt's disease, which also may be associated with ocular symptoms, including iritis and deafness. However, unilateral or bilateral seventh nerve paralysis is usually present in Heerfordt's disease, as well as other neurological signs.

Another nonsyphilitic entity which combines ocular and vestibuloauditory symptoms is the Vogt-Koyanagi syndrome (uveitis, alopecia, poliosis, and deafness). Vision is always decreased, and Parker [7] reported hearing impairment in 69%. The associated alopecia, poliosis, and vitiligo distinguishes this syndrome, and, in addition, evidence of hypothalamic involvement is also sometimes present.[8]

* Grennan, H. A., and Rones, B.: Personal communication to the author.

A related syndrome, Harada's disease, also includes all of the above, but, in addition, cerebral involvement and increased cells and protein in the spinal fluid are present.

The cause of Cogan's syndrome remains speculative. Infection due to an unidentified virus has been suggested, and Rosen [9] reported a case following vaccination, from which he inferred that the syndrome may represent an atypical postvaccinal encephalitis. Oliner † and co-workers have observed a case with pulmonary findings and report a well-documented case of Cogan's syndrome associated with periarteritis nodosa.[3] They suggest a causal relationship and emphasized the role of allergic mechanisms which may underlie the basic pathogenesis. In support of the allergic genesis is the frequent presence of eosinophilia in Cogan's syndrome, as demonstrated in the case reported here. However, no history of allergic diathesis in the patient or in the family was elicited.

The course is chronic, marked by remissions and exacerbations, and treatment as reported in the meager number of cases has been uniformly ineffectual. In this case empirical use locally of cortisone drops did not appear to influence the interstitial keratitis. After the neurological examination justified the diagnosis of Cogan's syndrome, a course of cortisone was instituted. The total eosinophile count of 500 dropped to 28. There was slight increase in appetite and weight, but no complications appeared. After about one week, the corneas cleared considerably, photophobia and epiphora disappeared, and vision in the left eye, which was 20/200, became 20/80. Vision in the right eye stayed at 20/50. Repeated examinations of the vestibuloauditory system revealed no significant change.

On the assumption that their patient's symptoms were the result of a vasomotor disturbance, Mogan and Baumgartner [10] performed a bilateral cervical sympathectomy. They reported improvement, but Donald and Gardner [5] were unable to duplicate their results in one other patient. Robson,[11] reporting another case, the fourth so treated, also found cervical sympathectomy ineffectual and concluded that this procedure is without rationale and contraindicated.

Other unsuccessful therapeutic measures include a single transfusion of convalescent plasma, in one case; prolonged intravenous administration of histamine, in another, and multiple vitamin therapy, in another.

SUMMARY

The 17th case of Cogan's syndrome, the first in a child, is reported. The entity consists of a triad of bilateral interstitial keratitis, involvement of both components of the eighth nerve with progressive bilateral deafness, and consistently negative serological and clinical evidence of syphilis. Other features usually associated with this syndrome are leucocytosis and eosinophilia. The etiology is unknown. Oral treatment with cortisone was associated with mitigation of the ocular signs and symptoms, the vestibuloauditory functions remaining unchanged.

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PERIVASCULAR ENCEPHALOLYSIS

Histopathology and Pathogenesis

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THE TRADITIONAL conception that necrosis or dissolution of cerebral tissue in patients having cerebral vascular disease is due solely to vessel obstruction is rapidly being changed. Furthermore, the speed at which so-called "vascular lesions" develop in various areas of the brain is now being considered in terms of inherent tissue vulnerability or resistance to noxae, oxidative processes, tissue-vessel exchange of metabolites, the "systemic factor," and the implicit "vascular factor." *

The prime interest in this communication is to develop the relationship of the lesions described here as "perivascular encephalolysis," and their pathogenesis in terms of (1) structural vascular alterations with special reference to the perivascular space, (2) the effect of systemic diseases upon cerebral metabolism and the accumulation of cellular effete products in the perivascular spaces, and (3) the development of an encephalolytic substance resulting from the influence of these perivascular metabolites upon the tissue enzyme balance presumably residing in the myelin-oligodendroglial system.

REPORT OF CASES

CASE 1.—L. R., a 78-year-old woman, was admitted to the hospital with the diagnosis of diabetes mellitus and dry gangrene of the left heel. She died 10 days after admission, and the findings at autopsy were generalized arteriosclerosis, arteriosclerotic aneurysm of the abdominal aorta and right iliac artery, cardiac hypertrophy, dry gangrene and ulceration of the left heel, and pulmonary infarct. Grossly, the brain showed considerable atrophy and advanced atherosclerosis of the vessels at the base. Histologic preparations disclosed moderate loss of cortical ganglion cells in lacunar acellular areas. Throughout the cortex and subcortical gray nuclei many ganglion cells revealed chronic cell disease. There were multiple small areas of perivascular cystic liquefaction necrosis involving mainly the subcortex and the subcortical gray nuclei. The small- and medium-sized vessels appearing in the center of these areas showed hyalinization and hyaline-fibrinoid degeneration. The first illustration, a myelin sheath stain of the lenticular nucleus and surrounding structures (Fig. 1), shows the numerous small cystic areas. However, despite the presence of advanced atherosclerosis of the large vessels and the changes observed in the smaller vessels, there were no areas of softening with gitter cell formation. Instead, as shown in the second illustration (Fig. 2), these lesions largely consist of a centrally or eccentrically situated vessel surrounded by a cystic cavitation, through which trabecu-

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lae may occasionally be seen. The third illustration (Fig. 3) demonstrates what may be considered the first stage of this process. This vessel, demonstrating hyaline-fibrinoid degeneration, shows a perivascular accumulation of oligodendroglia, astroglia, and inactive microglia cells. Compound granular corpuscles are not present. The next phase is represented by the fourth illustration (Fig. 4), which shows the perivascular oligodendroglial reaction plus beginning lysis of the neighboring tissue, again without the presence of gitter cells. The third stage is seen in the fifth illustration (Fig. 5), characterized by the disappearance of perivascular glial

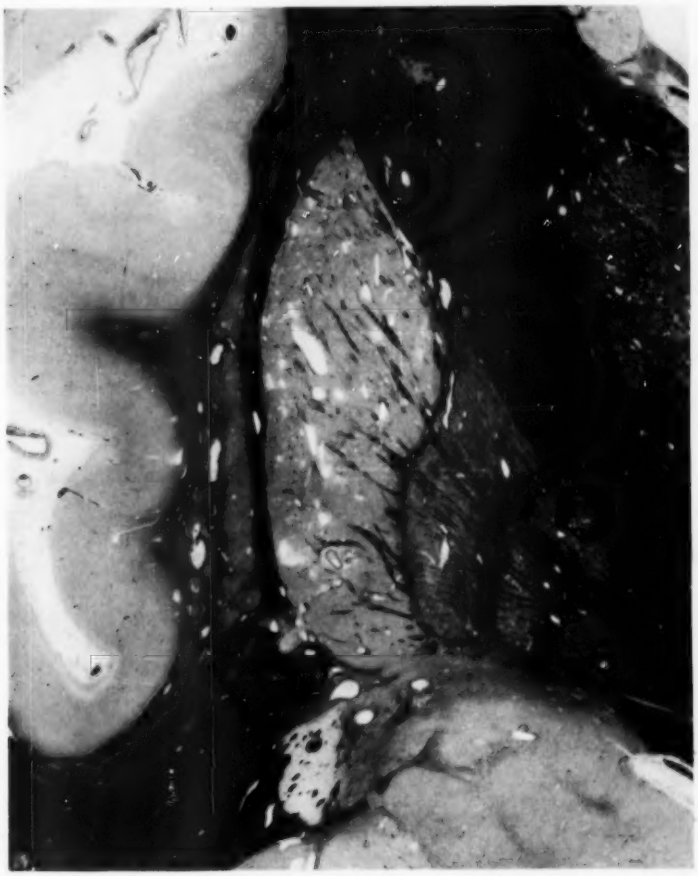

Fig. 1.—Lenticular nucleus and surrounding structures showing smooth-walled perivascular cystic encephalolysis. Weil stain; × 4.8.

elements but with an increasing amount of tissue lysis and liquefaction necrosis. Finally, the more fully developed perivascular cystic necrosis, as demonstrated in the second illustration (Fig. 2), constitutes the maturing or mature lesion.

Case 2.—M. T., a 58-year-old woman, was admitted to the Delaware State Hospital Feb. 19, 1951. She was one of five siblings. One sister died of a senile mental disorder. Her mother had diabetes. The patient was married three times. The first two husbands died and she was divorced from the third. During 1942 she began to show a change of personality and developed speech difficulties and aphasic phenomena. There was progressive mental deterioration, incon-

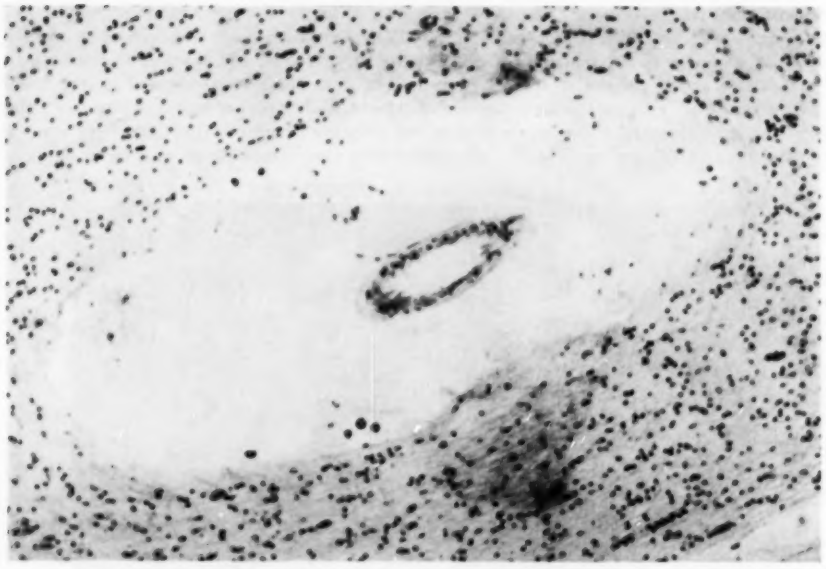

Fig. 2.—Putamen, showing perivascular cystic formation without gitter cell activity. Note the intense oligodendroglial proliferation of the surrounding tissue; final stage of process. Toluidine blue stain; × 112.

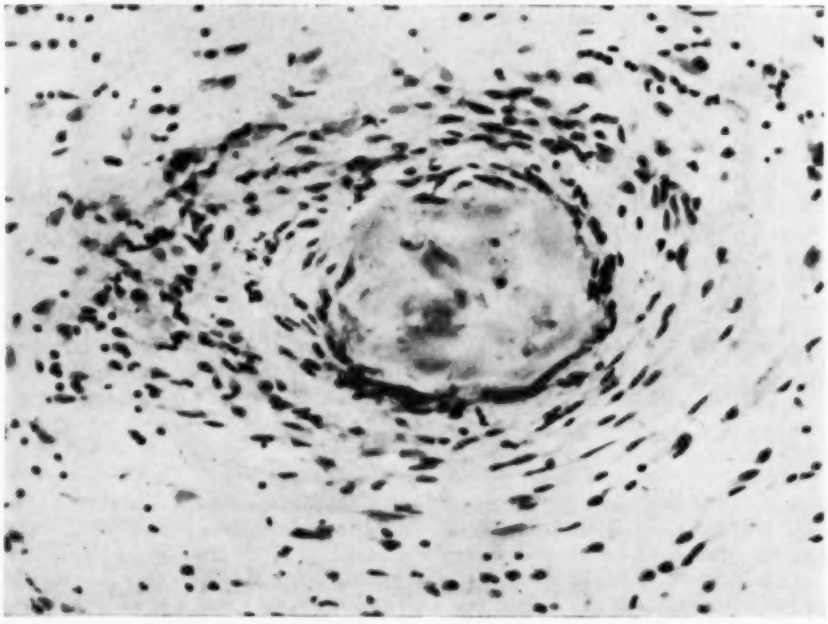

Fig. 3.—Putamen, first phase; obliteration of perivascular space by glial proliferation; marked oligodendroglial proliferation; moderate increase of astroglia. Toluidine blue stain; × 275.

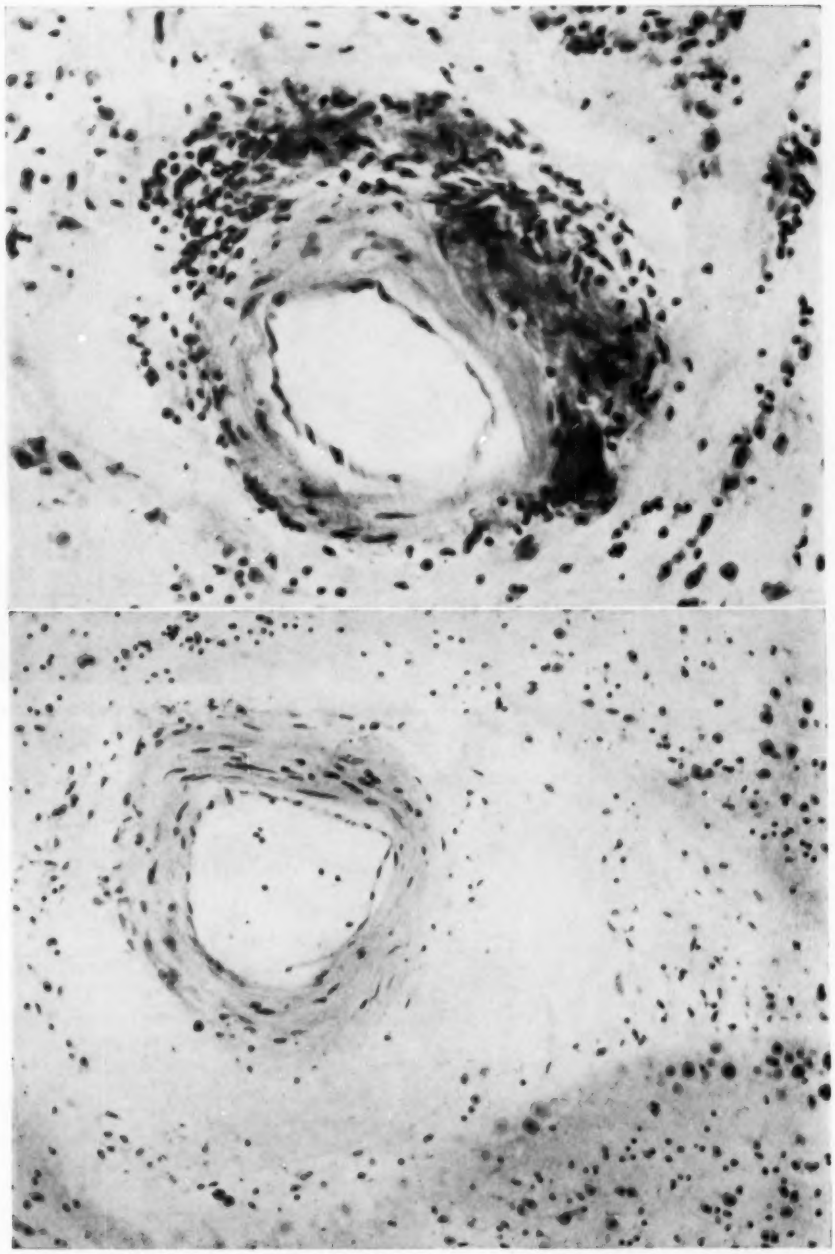

Fig. 4.—Second phase; small vessel showing hyaline change with perivascular proliferation of oligodendroglia, obliteration of Virchow-Robin space, and beginning lytic action on surrounding tissue by liberated enzymes. Toluidine blue stain; × 275.

Fig. 5.—Third phase, an extension of Phase 2, with disappearance of glial elements in the adventitial spaces but continuing lysis of tissue surrounding the vessel. Absence of gitter cells. Toluidine blue stain; × 275.

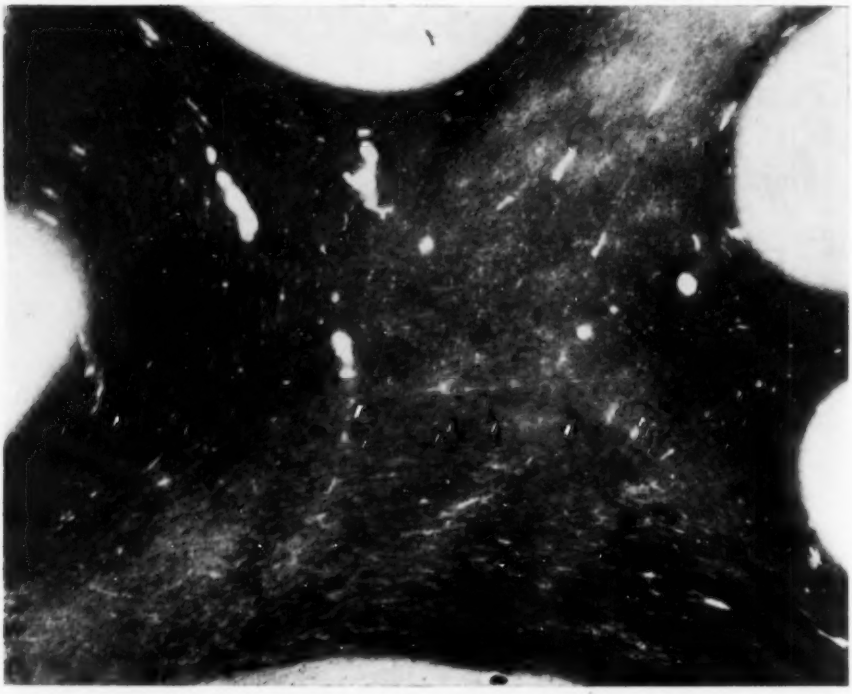

Fig. 6.—Frontal lobe, with patchy areas of demyelination and perivascular cystic demyelination. Weil stain; × 10.

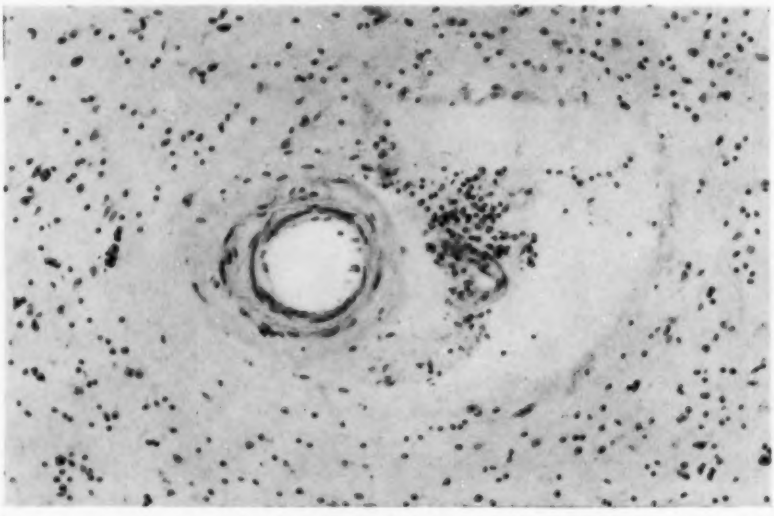

Fig. 7.—Subcortex of frontal lobe, with hyalinized vessel with perivascular oligodendroglial proliferation and developing lysis of tissue. Note absence of gitter cells. Toluidine blue stain; × 150.

tinence of bowel and bladder, unpredictable behavior, silly irrelevant conversation, global disorientation, and indifference to her environment. Physical and laboratory examinations were negative, with the one exception of moderately advanced diabetes mellitus. Electroencephalographic studies were reported as "within normal limits." She sustained a fractured hip on June 23, 1952. After operation, she developed cardiac failure and died July 1, 1952. Clinical diagnosis was presenile psychosis, Alzheimer's type.

Gross examination revealed an extremely small brain with a very characteristic predilective atrophy of the frontal lobes and the rostral aspects of both temporal lobes. This atrophy was sharply demarcated just rostral to the Rolandic area. The basilar vessels were of good size and were fibrotic. Coronal section through the brain disclosed a very pronounced atrophy of the cortex of the frontal lobe and the rostral portion of the temporal lobe. The insula of both

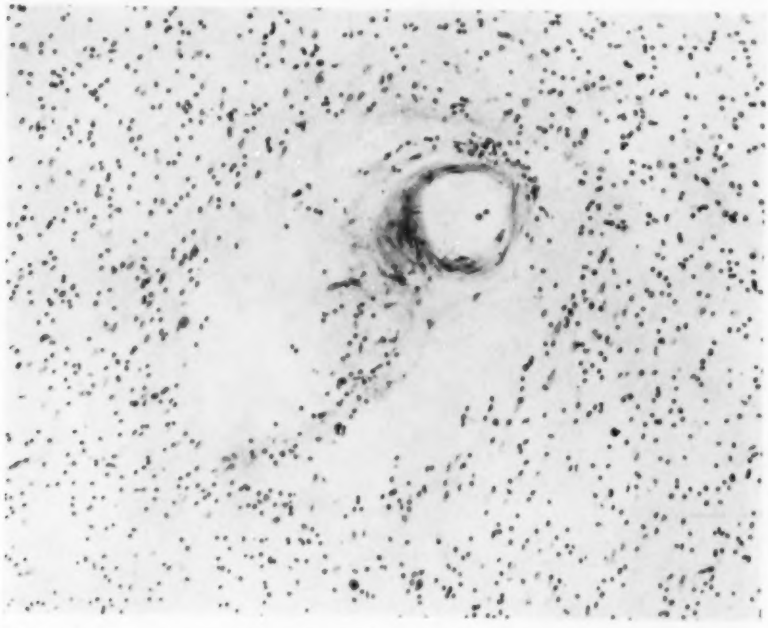

Fig. 8.—Subcortex frontal lobe, with bridge of tissue between Virchow-Robin space and surrounding parenchyma, containing oligodendroglia continuous with oligodendroglial proliferation in neighboring tissue. Lysis of tissue advancing. Toluidine blue stain; × 150.

hemispheres was greatly enlarged. There was an asymmetrical dilatation of the lateral ventricles. The gross diagnosis was idiopathic circumscribed presenile cerebral atrophy, or Pick's disease.

The myelin sheath stain revealed an intense atrophy of the frontal and temporal cortices. The subcortex, likewise, was atrophic and showed diffuse demyelination of a moderate degree. There were numerous perivascular areas of sharp demyelination, with lytic changes in the frontal and temporal lobes and in the striatum. Similar perivascular changes were seen in the pons and the medulla. The cortex of the frontal and temporal lobes was greatly narrowed, and there was a pronounced dearth of ganglion cells in the first three layers. Many of the large ganglion cells showed inclusions which displaced the nucleus. These were present both in the Nissl stain and in the silver stain, the latter showing the argentophile inclusions clearly. Chronic cell disease of the ganglion cells was frequent, and there was a marked increase of astroglia throughout the cortex. The subcortex showed an intense gliosis. Many of the small vessels of the cortex, subcortex, and basal nuclei showed hyaline-fibrinoid degeneration and frequently were in the center of an area of perivascular liquefaction necrosis. Ganglion-cell

loss and severe cell disease were observed in the dentate nucleus and in the olivary bodies of the medulla. Most of the large vessels were intact and showed mild metachromatic staining of the media. The basilar artery showed a mild subintimal proliferation of fibroconnective tissue.

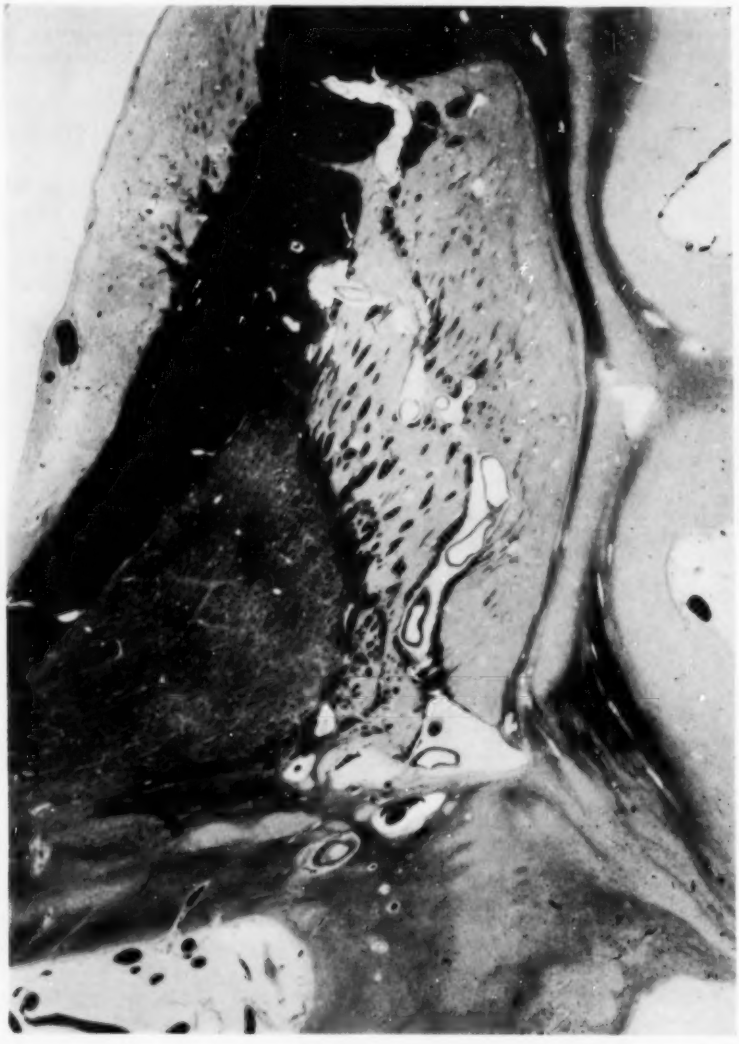

Fig. 9.—Lenticular nucleus, with perivascular cystic encephalolysis. Weil stain; × 7.

Figure 6, a Weil preparation, shows the characteristic appearance of the subcortex in the frontal lobes, and this was present, likewise, in the subcortical white matter elsewhere. Figures 7 and 8, showing Nissl-stained preparations, disclose the intense degree of oligodendroglial and astroglial proliferation in the vicinity of small vessels, the latter presenting hyaline and hyaline-fibrinoid mural change. There is a perivascular liquefaction necrosis with lysis of

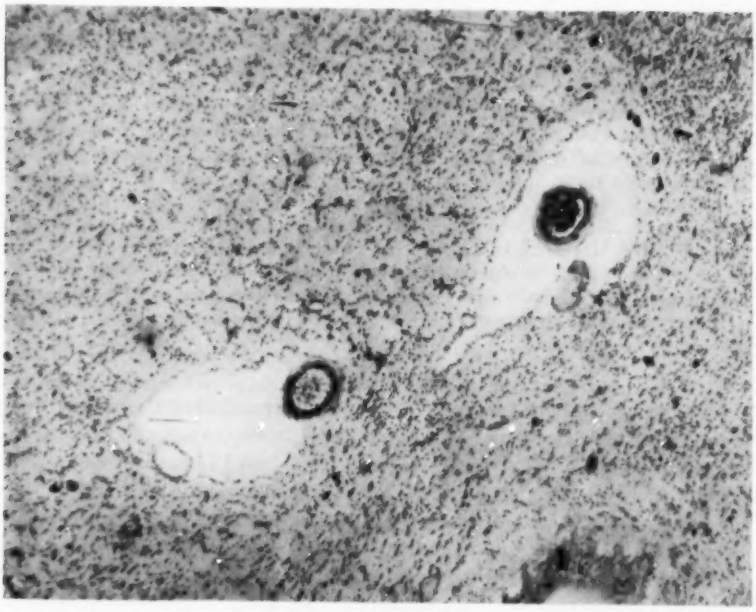

Fig. 10.—Putamen, with two vessels showing hyaline-fibrinoid change with perivascular lysis. Intense oligodendroglial proliferation in adjacent tissue; no compound granular corpuscles present. Toluidine blue stain; × 56.

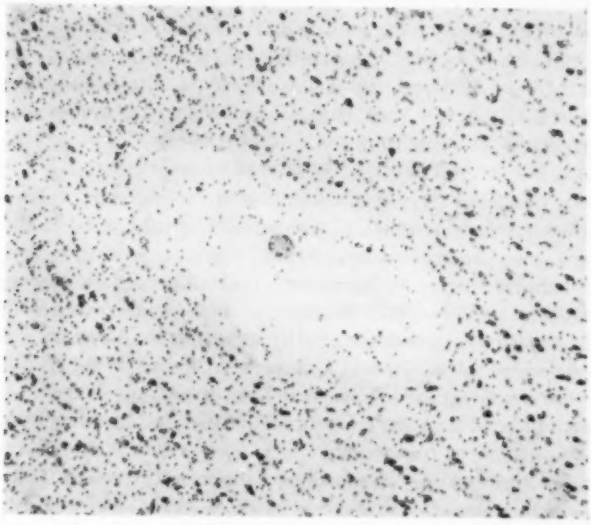

Fig. 11.—Temporal lobe, showing developing final phase of perivascular lysis with few trabeculae traversing cystic area. Toluidine blue stain; × 75.

perivascular tissue. Numerous oligodendrocytes can be seen adjacent to the vessel wall, and in Figure 8 there is a bridge, containing oligodendrocytes, between the perivascular Virchow-Robin space and the surrounding parenchyma. There are no macrophages or gitter cells present. Figure 9 is a myelin-sheath preparation of the lenticular nucleus and surrounding structures, showing the pronounced involvement of the putamen with large perivascular cystic areas, the margins of which are rather regular and smooth. Figure 10 illustrates two vessels lying in the putamen, the walls of which show definite hyaline-fibrinoid change. The parenchyma surrounding the perivascular cystic areas is richly infiltrated with proliferated oligodendrocytes and, to a less extent, with astrocytes. There are no gitter cells in the vicinity. Figure 11 shows an intermediate process in the temporal lobe, in which a small vessel can be seen in the center of an area of liquefaction necrosis, with a lytic process breaking down the perivascular parenchyma. Several fine trabeculae of remaining parenchymal tissue can be seen bridging the cystic space. Here, again, the subcortex shows a pronounced oligodendroglial proliferation and hypertrophy. Compound granular corpuscles are not present. Inflammatory elements are not witnessed in the perivascular spaces.

COMMENT

The lesions which have been described and illustrated here are not "acute cystic softening," perivascular edema, Nissl's *Schrumpfräume,* or contraction spaces, or artifacts. The completely developed lesion (Figs. 2 and 11) may remotely resemble these only at first glance; however, the various stages leading to the mature lesion may be found in some individual cases. The stage of development of the perivascular glial reaction and the subsequent perivascular encephalolysis is dependent upon (1) the preparation of the perivascular area by toxic and/or hypoxic factors, (2) the duration and intensity of the perivascular metabolic and enzyme activity, and (3) the degree of vulnerability of the perivascular tissue.

It must be recalled that, in addition to structural vascular abnormalities, both of these patients had diabetes, with its attendant metabolic aberrations; one had gangrene, with the probable generation of toxic substances and altered function of the endocrine system, and, again, both had faulty dietary regimens and failing cardiovascular systems. Combined, these factors provoke altered cerebrovascular resistance, disordered cerebral tissue metabolism, faulty elimination of cerebral tissue catabolites, derangement of enzyme and coenzyme systems, and increased vulnerability of cerebral tissue to noxae. All of these factors probably were responsible in varying degrees for the type of lesions described here.

The factor of cerebral oxygen consumption in the presented cases is significant, and this justifies a brief discussion of the variables encountered in the relationship of cerebral oxygen consumption to cerebral vascular resistance and blood flow. It has been noted that, despite an increase of cerebral blood flow, observed in diabetic coma and thiopental (Pentothal) anesthesia, there is decreased cerebral oxygen consumption in both these conditions.[1] Decreased cerebral oxygen consumption is found in conditions in which there is a decreased cerebral blood flow, such as cerebral vascular disease, heart failure, increased intracranial pressure, myxedema, pernicious anemia, diabetic acidosis, thiopental narcosis, and neurosyphilis, and during the use of corticotropin or cortisone.[1]

The effect of accumulating tissue catabolites, resulting from faulty metabolism and transport and from disturbed enzyme systems, likewise may have played a role in the formation of the lesions described here. Older people have food fads, with vitamin deprivation,† and the latter is common among diabetics.

† References 2 and 3.

Peters and Thompson [4] showed that more pyruvate accumulates in preparations of respiring brain tissue from avitaminous pigeons than in similar preparations of normal brain, and that this extra accumulation can be prevented by the addition of small amounts of thiamine HCl to the brain preparations. Peters [5] concluded that thiamine acts as a coenzyme, or part of a coenzyme, of the pyruvate-oxidase system. Deficiency of this vitamin results, therefore, in a block in the series of energy-yielding reactions whereby glucose is oxidized by the cells; its breakdown proceeds as far as pyruvic acid, which, since its further oxidation is inhibited, consequently accumulates. The importance of the pyruvate-oxidase system lies in the fact that utilization of oxygen by most tissues is dependent on its integrity, and failure of this system results in virtual tissue anoxia.

These predisposing or "systemic factors" were present, in addition to vascular changes, in both cases presented here. The effects of a toxianemic "system factor" upon cerebral tissue has been reported by Ferraro, Arieti, and English,[6] who demonstrated the cerebral changes in the course of pernicious anemia and showed, among other pathological changes, illustrations of discrete areas of demyelination, endarteritis of the medium and smaller vessels, and perivascular glial proliferation.

Hurst,‡ in a number of contributions, has reviewed the work on experimental demyelination and its relation to human and animal demyelinating disorders. In the former, it has been observed that in allergically induced encephalomyelitis there may be a concentric proliferation of the adventitial cells of the small vessels, tending to obliterate the Virchow-Robin spaces.[11] Thus, noxae of anaphylactic origin affect, in a conspicuous manner and in varying degrees, the immediate perivascular structures. Demyelination may also follow after a variety of experimental procedures which, in one way or another, bring about an interference with the normal oxidative requirements of brain tissue.

A unique method of cerebral microembolization was devised by Lewis and Swank [12] in the experimental animal so that a transient minimal insult to the tissue would result in stimulating cells, rather than causing their degeneration. Their study was prompted by the observation that an increase of perivascular oligodendroglia has been described in certain hypoxic conditions,§ in encephalitis,[14] in pernicious anemia,[6] in lead poisoning,[15] and in Huntington's chorea.[16] They observed that after transient impairment of the cerebral circulation definite glial changes occurred in the neighborhood of blood vessels. There was proliferation and hypertrophy of the oligodendroglia after initial mild acute swelling and oligodendroglial response following minimal ischemia, whereas after severe ischemia there was an astrocytic proliferation. The authors speculated "that such lesions might both interfere with normal metabolic exchange between the blood stream and the parenchyma and alter the normal elasticity of the vessels." They found the lesions more frequent in the white matter. A significant statement by Lewis and Swank was that "multiplication of perivascular oligodendroglia has been noted in several conditions in all of which some disturbance in nutrition can be assumed to occur.—It seems possible that transient ischemia due to fat embolism, sludged blood, stasis, and transient vasospasm, or perhaps to aggregation of platelets, red blood cells, or chylomicra,[17] might produce similar perivascular glial lesions in the central nervous system."

‡ References 7 through 10.

§ References 7 and 13.

Their illustrations showed perivascular accumulation of oligodendrocytes, some of which were in the process of division. The appearance of these lesions is similar in many respects to the first phase, as described and illustrated here, in which there is considerable proliferation and hypertrophy of perivascular oligodendroglia. This would correspond to the initial phase of ischemia, following which the train of events leading to disturbed enzyme balance would proceed. Lumsden [18] also embolized 150 rats by intracarotid injections of coagulants and produced "multiple acute softening" lesions which in no way resembled those produced in cyanide demyelination.

Analogies to the foregoing experimentally induced perivascular demyelination may be had in a variety of conditions in the human, as already alluded to in the literature. In addition to numerous toxic agents which may induce cerebral ischemia, there has been described more recently by Corday, Rothenberg, and Putnam [19] a condition known as cerebral vascular insufficiency, in which the authors explain some types of localized cerebral encephalopathy as being due to a number of predisposing factors. Among these are hemorrhagic shock, hypotension due to coronary shock, surgical and traumatic shock, hypotension due to sympathetic block, postural hypotension, carotid sinus stimulation, and spinal anesthesia. Greenfield [20] and Broman [21] have indicated that edema can damage the surrounding parenchyma and in all probability has a selective action upon the myelin sheaths and oligodendroglia.

Schaltenbrand,[22] in his study of the perivascular spaces, cited Cushing as having thought that they acted as lymphatic spaces evacuating waste products from the nerve cells into the subarachnoid space. Schaltenbrand [22] found that the Virchow-Robin spaces existed only around the larger vessels of the brain and that only a little connective tissue surrounded the capillaries. In his study he concluded that very little fluid could be discharged from the perivascular spaces into the subarachnoid space, and that substances exchanged between the brain tissue and the vessels pass only through the vessel wall and the surrounding glial tissue. Burrows,[23] as a result of his observations in carefully correlating the symptoms of poliomyelitis with the postmortem findings in a large number of cases, regarded the perivascular spaces of the central nervous system as similar to the lymphatic spaces elsewhere in the body. He considered the pressure of the exudate in the perivascular spaces as the cause of the destructive changes occurring in the ventral horn cells in poliomyelitis. Thus, physical pressure or chemical action may singly, or in combination, be responsible for interference with oligodendroglial enzyme function.

Lumsden,[18] in discussing the subject of experimentally induced cyanide leucoencephalopathy, noted that all the assembled evidence is contrary to a simple vascular or asphyxial explanation. He further stated that the cyanides are toxins which have a special affinity for the central white matter of the brain and are potent enzyme poisons. As such, the cyanides presumably disturb the enzyme mechanism, present in the myelin sheath and in the oligodendroglia, which appears to play a role in the enzyme balance between the myelin sheath and the parenchyma as a whole. It is to be noted, however, that the cyanide lesions develop suddenly and are progressive, a phenomenon which Hurst [7] first observed. From this it may be concluded that the demyelination is a secondary process which is continuous, and that the toxic or lytic agent which damages the white substance is one derived from within the white matter itself, rather than resulting primarily from the cyanide. Lumsden [18] presented additional data and references in the literature supporting

the concept of a ferment hypothesis of spontaneous demyelinating diseases. In some of the perivascular demyelinating disorders there is a real probability that vascular stasis will in itself produce necrotic lesions, partial as well as complete demyelination of the parenchyma without primary thrombosis.

Thrombotic lesions with the accompanying softenings and phagocytic activity were not seen in the histological preparations of either brain described here. Instead, the phases of subcortical perivascular gliosis, consisting of oligodendroglial and astroglial proliferation, initial perivascular liquefaction necrosis or encephalolysis, oligodendroglial disintegration, and slowly progressive and fairly uniform liquefaction of perivascular tissue were found.

Finally, what is the substance specifically responsible for the perivascular lytic action upon a cerebral tissue already made vulnerable by systemic and vascular factors? In 1941, Winkelman and Moore [24] reported a case of progressive degenerative encephalopathy occurring in infancy with antenatal onset, in which there were present multiple cystic softenings of the brain, not of vascular origin. We showed the striking likeness of this condition to that of "swayback" of lambs, a disorder, according to Innes and Shearer,[25] presumably due to the lack of trace metals in the diets of pregnant ewes, and suggested that the subcortical tissue lysis resulted from some toxic substance, perhaps similar in its origin to that of "swayback." Lumsden,[26] who reported a case identical to ours, in his discussion and conclusions offered a thought-provoking and plausible hypothesis regarding the development of the cystic cavitations. He stated that "a metabolic toxin, or even asphyxia alone," causing parenchymal damage may, at any age, give rise to the formation of an autolytic enzyme. As to the source of this enzyme, he said:

> This lytic ferment may be produced by the disintegrating myelin sheath itself and be neutralized in the ordinary course of events by some secretion from the oligodendroglia. In the absence of such an oligodendroglial antiferment, myelinosis and liquefaction, once initiated (by any noxa) would proceed unhindered.

The cystic lesions reported by Lumsden and us were considerably larger than those reported here, but the difference in the mechanism may be quantitative rather than qualitative, and due to the intensity and duration of the action of the toxic and myelinolytic substances.

SUMMARY AND CONCLUSIONS

A morbid process of perivascular demyelination and cystic liquefaction necrosis in the brain is here described as "perivascular encephalolysis," in view of the presented concept of the development of a lytic agent in the perivascular space and its effect upon the surrounding tissue.

The pathogenesis of the lytic substance is predicated upon the appearance and description of the perivascular lesions, shown in the illustrations, and upon the data submitted from the literature.

The generation of this lytic material appears to be dependent upon a chain of circumstances consisting of (1) structural alterations of the small vessels of the brain, (2) the development of tissue vulnerability due to the "systemic factor," (3) the accumulation of catabolites in the perivascular space, and (4) the consequent imbalance of the myelin-oligodendroglial enzyme system, resulting in the formation of an encephalolytic substance.

It is inferred from the presented material that these specific lesions should not be regarded as the cystic softenings of the older nomenclature, resulting from occlusion of small vessels with gitter cell formation.

Finally, the inherent clues to preventive measures may be found in the factors leading to the development of perivascular encephalolysis.

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EFFECT OF INTRACAROTID IODOPYRACET (DIODRAST) UPON CEREBRAL BLOOD FLOW

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DURHAM, N. C.

PREVIOUS anatomical studies have revealed that it is possible to produce severe cerebrovascular injury following the intracarotid injection of iodopyracet (Diodrast).* This injury is characterized by striking vasodilatation and progressive changes in vascular permeability, as well as evidence of stasis of blood flow with accompanying edema and hemorrhage. Because of the discrepancy in these observations and the prevailing view that arteriographic accidents are vasospastic in nature, it was thought worth while to attempt a corroboration of these anatomical findings by means of physiological experiment.

METHODS

The experimental animals were healthy, young adult rabbits and Macacus rhesus monkeys. During the period of surgical preparation, light intravenous pentobarbital (Nembutal) anesthesia was used for all rabbits and one monkey. In the remaining monkeys light ether-oxygen mixtures were used. The right common carotid artery was exposed and cannulated. The external carotid artery was ligated in the rabbit preparations. A femoral artery and vein were also exposed and cannulated.

During each experimental period the animals were curarized and mechanically respirated and stable basal observations obtained. Blood pressures were recorded by direct measurement with a closed-system mercury manometer. Electroencephalograms were recorded from bipolar leads on a Grass six-channel electroencephalograph. In the monkeys the cerebrospinal fluid pressures also were recorded from cisternal punctures (#20-gauge needle) with the Sanborn electromanometer.

For estimates of qualitative changes in blood flow, a modification of the Gibbs [3] heated thermocouple technique was used. The thermocouples were placed as precisely as possible in the cortex, usually in the parietal region, through two millimeter twist-drill holes placed in the skull. Each cold reference junction was placed in an adjacent area of the same cortex. The thermocouples were connected in series to mirror-string galvanometers of a suitable sensitivity. Deflections were read directly from a scale 1 meter from the deflecting mirror.

Iodopyracet in 35% and 70% solutions was injected in amounts ranging from 0.5 to 5.0 cc. and at rates varying from 0.05 to 1.0 cc. per second. Prior to each injection positive increases in blood flow, as indicated both by the thermocouples and by rises in cerebrospinal fluid pressure, were observed as CO_2 was added to the inspired air. Before each iodopyracet injection, an injection of Ringer's solution, similar with respect to amount and rate, was made as a control. At the end of a set of experiments, each animal was given, intravenously, from 100 to 300 mg.

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* References 1 and 2.

of the tetrasulfonic acid copper phthalocyanine and, after 20 minutes, was killed by stopping the respirator. Brains were removed immediately and examined for evidence of vital staining with phthalocyanine, and the exact thermocouple locations were determined. The thermocouple placement was found to vary somewhat in location but was relatively uniform with respect to depth.

The EEG changes following iodopyracet have been previously described [2] and will not be further discussed here. The results in those animals showing seizure electroactivity were excluded from the accompanying charts, since it was felt that indications of increased blood flow under these circumstances might be due to the seizure rather than to the effect of iodopyracet upon the cerebral vessels. Previous experience had indicated that severe vascular damage could be readily recognized in the electroencephalogram.[2] Therefore with EEG control it was possible to use a single animal for several observations.

The charts do not include results obtained from those animals with severe injury to the blood-brain barrier as evidenced by the dye indicator technique.

TABLE I

IPSILATERAL BLOOD FLOW	
INITIAL FLOW (1 Minute)	5 MINUTE FLOW (2 - 5 Minutes)
20	20
8	
12	20

TABLE II

CONTRALATERAL BLOOD FLOW	
INITIAL FLOW (1 Minute)	5 MINUTE FLOW (2 - 5 Minutes)
12	12
3	2
9	10

DECREASE

INCREASE

RESULTS

Blood Flow.—Changes in blood flow in response to iodopyracet as indicated by the heated thermocouple technique may be divided into two phases: (1) the immediate qualitative response to injection, and (2) the average qualitative change during the second through the fifth postinjection minutes.

Of 20 observations of the cerebral blood flow in the injected hemisphere, 60% showed an initial increase in flow, while in 40% there was an initial decrease in flow (Table I). This decrease was always relatively small in magnitude and short in duration. The initial increase in flow was recorded in 8 of 11 instances in the rabbit, and in 4 of 9 in the monkey. On the other hand, in all instances the flow of the injected side was increased after the first 60 seconds (Table I).

Twelve studies were made of blood flow in the hemisphere contralateral to the injection. Of these, nine, or 75%, indicated an initial increase in flow. Ten of the 12,

or 83%, were increased after the first minute (Table II). In this group only two observations were made upon the rabbit, and in both an increased flow was noted in the contralateral cortex.

In all, 32 observations of blood flow were tabulated, and 30, or approximately 94%, indicated increased blood flow at once, or within one minute following the injection of iodopyracet. In each instance of convulsive cerebral electroactivity, blood flow increases were recorded. When there was evidence of severe vascular damage in the EEG or when the blood-brain barrier became permeable to the anionic dye, the blood flow was decreased.

Cerebrospinal Fluid Pressure Changes.—Changes in cerebrospinal fluid pressure are represented in Table III. It may be noted that there was but little difference in the response to Ringer's solution and to iodopyracet. After injection of Ringer's solution the initial increase averaged 6.3 mm. of water (range, 2 to 20 mm.) and the initial decrease averaged 7 mm. of water (range, 4 to 10 mm.). Intracarotid

TABLE III

CEREBRO SPINAL FLUID

PRESSURE

	INCREASED	DECREASED	DIPHASE ↑↓	NC CHANGE	TOTAL
RINGER'S CONTROL	13	4	1	3	21
DIODRAST 35 & 70%	11	5	5	1	22

iodopyracet occasioned an average initial rise of 8 mm. of water (range, 1 to 25 mm.) and an initial fall averaging 5.6 mm. of water (range, 2 to 10 mm.). The diphasic response to both iodopyracet and Ringer's solution consisted of an average rise of 7 mm. of water, followed by an average fall of 4 mm. of water below the initial level. This type of response was transient and usually complete in 30 seconds.

In the present observations, there appeared to be little relationship between the effect upon cerebrospinal fluid pressure and either the amount or the rate of injection. All decreases in cerebrospinal fluid pressure were observed after the use of 70% iodopyracet. On three occasions the effect of injecting 35% iodopyracet was studied. This concentration twice caused elevations in the cerebrospinal fluid pressure, while once it produced no essential change. These pressures generally returned to the preinjection level within three minutes.

In only two situations was there direct correlation between alterations in blood flow and the cerebrospinal fluid pressure changes: When CO_2 was added to inspired air and when electrical fits occurred, increased values were recorded. The similarity in response of cerebrospinal fluid pressure to both the control injections of Ringer's

solution and the test injections of iodopyracet seems to preclude correlation of cerebrospinal fluid pressure changes with the blood flow responses observed after iodopyracet injections. Other unpublished observations indicate that the cerebrospinal fluid response to intracarotid injections is altered by the osmotic pressure of the solution.

Blood Pressure.—Blood pressure changes were of small magnitude and bore no significant relationship to the cerebral blood flow.

COMMENT

In general, the reactions of 35% and 70% iodopyracet were only quantitatively different with respect to dosage required to produce injury. Though evidence for an immediate decrease in cerebral blood flow in the injected cortex occurred in 43% of the experiments, since the immediate response was replaced in all instances by increased flow, it seems unlikely that persistent vasospasm plays a significant role in the production of neurologic sequelae following arteriography with iodopyracet. Furthermore, profound decreases in flow are seen only as a delayed response when sufficient iodopyracet has been administered to produce both severe EEG changes and blood-brain barrier alterations. Microscopic studies [2] at this stage disclose concomitant vasodilatation, stasis, hemorrhage, and edema.

SUMMARY

Alterations in cerebral blood flow as studied by the heated thermocouple technique and cerebrospinal fluid pressure changes following intracarotid iodopyracet injections are presented.

Under the experimental conditions cited, the principal reaction to intracarotid iodopyracet in the rabbit and the monkey appears to be that of vasodilatation.

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IMPAIRMENT OF MENTAL FUNCTION DURING ELECTRIC CONVULSIVE THERAPY

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EXPERIENCE with electric shock treatment leaves no doubt in the mind of the clinician of the seriousness of impairment of mental function in patients subjected to this procedure. The severe mental disintegration caused by extensive shock treatment hinders all but the most superficial psychotherapy and, in addition, gravely interferes with the patient's social and occupational adjustment. Yet it is difficult to find a psychological test which would unequivocally and quantitatively express the obvious clinical deficiency.

Rylander [1] used a number of selected psychological tests to ascertain impairment of function of the frontal lobes following lobotomy and found the score of the Noun Enumeration Test persistently diminished as long as 28 months following the surgical procedure. It was therefore considered of interest to apply this test to patients receiving electric shock therapy.

METHODS

Patients treated by electric shock on an ambulatory basis were tested by a word-naming test one-half hour preceding each treatment. Directions for the word-naming test given in the Stanford-Binet intelligence test were followed, with the exception that the subjects were instructed to keep their eyes closed throughout the test to eliminate sensory visual cues and the duration of the test was extended to three minutes, instead of the customary one minute. The first test was considered as the pretreatment, baseline value, and subsequent tests were compared with this baseline. In the followup period after completion of a course of therapy, the patients were tested at intervals of two to four days, and one, two, three, four, and six weeks following the last treatment. Treatments were frequently given at one-day intervals in the beginning of shock therapy; later they were spaced at intervals of two or three days. The total number of treatments was determined by the clinical condition of the patient and consequently varied from patient to patient.

As a control group, 17 inpatients of the New York State Psychiatric Institute, admitted on voluntary application, were selected by the clinical staff not involved in the project, on the sole criteria that the patients were designated for shock treatment and that they would be cooperative to testing. These were the only criteria applied to the experimental group. The control group was tested 10 times, at the rate of 3 tests per week to determine whether a learning factor, found on repetition of the test in normal subjects, would also occur in a group of patients with mental illness.

The observations are based on the results obtained from 30 subjects who had a minimum of 5 consecutive treatments, spaced not more than four days apart, with a range from 5 to 13 treatments and with an average of 7.06 treatments. Three of these subjects had the "electronarcosis"

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Assistance in this study was rendered by James L. McCartney, M.D., who supplied the facilities and the services of his psychologist for testing of the treatment group, by Mrs. Jane H. Sturm, M.A., and Miss Marion Jacks, M.A., who assisted in the psychological testing, and by Philip Rhodes, B. A., who assisted in the statistical calculations.

modification of electric convulsive therapy. The 30 subjects were classified into the following diagnostic categories: manic-depressive psychosis, nine; involutional psychosis, five; schizophrenia, eight; anxiety state, two; psychoneurosis, obsessive-compulsive type, two; psychoneurosis, hysteria, one; psychoneurosis, hypochondriasis, one; reactive depression, two.

To test the possibility that patients requiring a greater number of treatments for clinical improvement might respond differently than patients requiring less treatment, the word scores of a group of 11 patients, all of whom had at least eight treatments, were compared with the scores of the remainder of the group, which received five to seven treatments. Since the differences were not statistically significant, the averages of the total group were used where applicable to achieve greater statistical reliability.

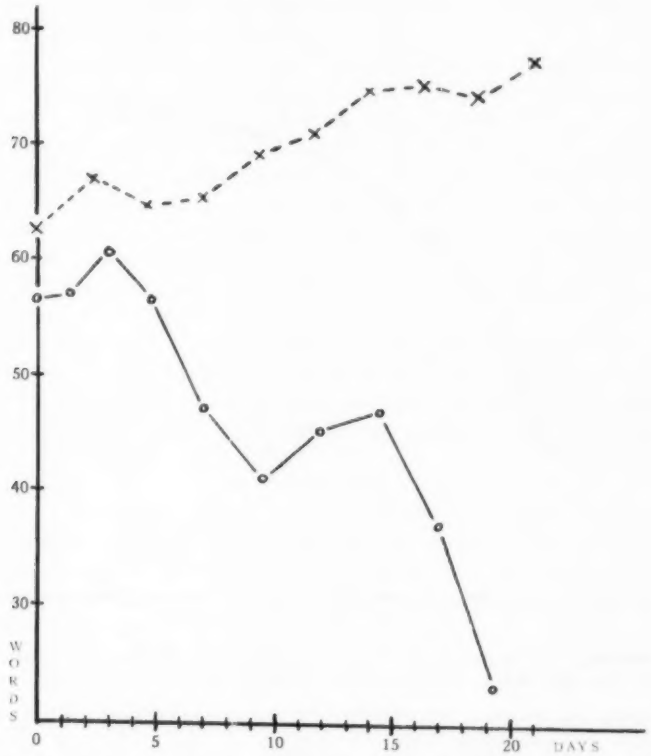

Chart 1.—Averages of word scores (left ordinate) of 30 patients treated with electric shock treatment (circles) and of 17 untreated (control) patients (crosses).

RESULTS

An initial increase in word score developed in 16 subjects after the first treatment. An increase in word score persisted in 11 subjects after the second treatment, thus causing the average score for the total group to rise slightly to a peak, which occurred after the second treatment (Chart 1). After the third treatment, a downward trend in the average word score set in. This downward trend prevailed in all but six subjects, who maintained a slight persistent increase in word scores up to the end of the course of treatment.

The downward trend in word scores reversed itself after the sixth treatment. Closer analysis of the phenomenon revealed that a remarkable reversal of the downward trend occurred in 10 subjects. A similar reversal of the declining trend occured also in five subjects after the fifth treatment and in two subjects after the seventh treatment. The individual reversals influenced the downward trend of the statistical averages, causing a slight rise in average word score after the sixth treatment (Chart 1).

The decreases from the pretreatment level became statistically significant at the 0.05 level after the fourth treatment and continued significant at the 0.01 level from the fifth treatment onward.

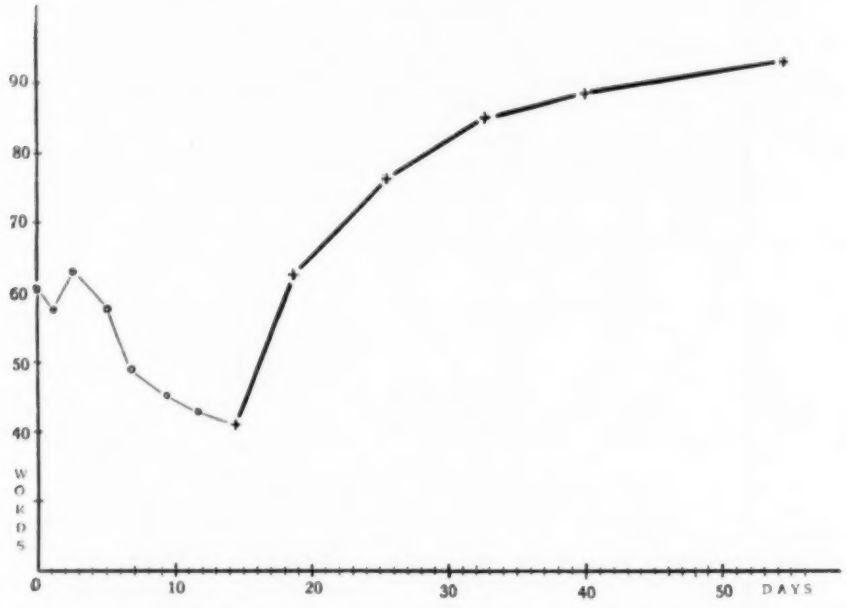

Chart 2.—Averages of word scores of 11 patients with a six-week follow-up period. Circles indicate shock treatment; crosses, follow-up tests without treatment.

In contrast to the treated group, the average scores of the control group did not diminish, but, rather, showed a mild, statistically significant increase (Chart 1). It was probably due not to coincidence but, rather, to the criteria of selection that the average word scores of the first test of both the treatment group and the patient group did not differ statistically, thus satisfying the criteria for samples drawn from a common population.

The word scores of the treated and untreated groups began to differ at the 0.05 level after the fourth treatment and continued to differ at the 0.01 level of significance from the fifth treatment to the end of shock treatment.

After termination of shock treatment, the word scores promptly rebounded and returned to the pretreatment levels within one week. The increase continued over the six weeks' observation period, gradually achieving a level significantly above that of the first test (Chart 2). Only 11 subjects could be included in the averages

of the follow-up group, since the remainder either discontinued follow-up visits or relapsed and had to be re-treated before completion of the six-week period.

A decrease in word score was conditioned on the time interval elapsed from the preceding shock treatment. As noted in the follow-up study, the initial preexperimental level was regained within seven days after termination of shock treatment. Even when the subject was retested on the fourth day following a shock treatment, the score returned to the approximate level preceding the individual treatment. If retesting was done on the fifth day, as, for instance, when the patient failed to appear for a treatment, the score invariably increased from the immediately preceding level. It was therefore necessary to discard from the study all subjects with an interval greater than four days.

A partial convulsion (Jacksonian type) or a petit mal response failed to evoke the fall in word score seen after a grand mal convulsion. There were 11 instances of petit mal or incomplete convulsion in the discarded cases of this series of patients. To determine the effect on the word score, the instances of incomplete response were divided into two groups according to the number of grand mal convulsions preceding the partial response. One group contained six subjects whose partial convulsions occurred during the first or second treatment. As noted above, the average word score of the total group increased by 4.5 words after the first two treatments. The average increase in the group of six subjects with a partial convulsion was identical—4.5 words.

The second group contained five subjects whose incomplete convulsions occurred in the range of treatment when the word scores of the experimental group were declining from the initial level. However, the patients with incomplete convulsions showed no decrease in word score, but, rather, presented an increase of 9.8 words.

COMMENT

The word-naming test appears to be an objective, quantitative, statistically verifiable test for the clinically observed impairment of mental function during shock treatment. The test is undoubtedly an expression of a complex, specifically human mental function, which involves not only remote memory and the ability promptly to recall memories but probably also drive, spontaneity, and initiative.

Loss of memory during shock treatment can be clearly demonstrated by memory tests of learning, recall, and recognition.* Yet the memory traces are by no means obliterated but, rather, just made unavailable for spontaneous recall. Memories of experiences or learned material are not recollected if asked for in a nondirective manner. However, the memories may be readily recognized if presented in detailed factual [4] or pictorial form.[3]

In addition to loss of memory, a reduction in spontaneity may contribute to the decrease in word scores during treatment. Retardation in formation of associations was observed after electric shock by Liberson [5] during a study of the word association test. The reaction time in patients treated by electric shock was almost double that of a control group.[5]

Proficiency in word test performance is lost only temporarily. It would seem that this faculty is made inaccessible to the patient rather than altogether lost. After completion of treatment, the ability to name words not only returns but even sur-

* References 2 and 3.

passes that of preshock level. The mechanism of the loss of function is in the nature of temporary suspension rather than deletion of the function. In this respect the loss of word-naming ability is comparable to other physiological changes during shock treatment, such as the temporary loss of sexual potency observed in male patients [6] and the temporary loss of menstrual function, observed in female patients.[7]

The curve representing the word-naming scores did not maintain a linear relationship to the number of shock treatments. Instead, the averages of the word scores receded through two phases: a beginning rise and fall to the fifth treatment and a secondary rise and fall after the sixth treatment. The biphasic appearance of the curve might be interpreted as indicating the possibility that two factors are involved in the production of the word scores. Each factor is probably modified by shock treatment in a different manner, or in differing intensities at different time phases of treatment, leading to a biphasic curve of regression.

SUMMARY AND CONCLUSIONS

The scores of a word-naming test decreased significantly after five or more electric shock treatments.

Recovery took place within one week following treatment, and the word scores continued to increase during the six weeks of observation after the termination of electric convulsive therapy.

A comparable control group of patients showed no decrease but, rather, a moderate increase in word scores on repetition of the test over a three-week period.

A petit mal or partial convulsion did not impair the word scores.

The decrease in word scores is interpreted in terms of temporary inaccessibility of the word-naming faculty during shock treatment.

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ELECTROENCEPHALOGRAPHIC CHANGES RESULTING FROM CAROTID ARTERY COMPRESSION

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THE VALUE of electroencephalography in clinical work is reflected in the vast literature which has developed on this subject since Berger's original report in 1929. It has become apparent, however, that if the diagnostic value of electroencephalography is to be extended, activation techniques must be developed and assessed. One must alter the resting tracing by physiological or pharmacological means if one is to obtain additional information. Although this was appreciated in part at an early stage in the case of hyperventilation, other methods of activation have been investigated only within the past few years. Such techniques must be studied in a systematic fashion if their indications, potentialities, and limitations are to be fully understood.

Among the various methods of activation being tried in our laboratory, cerebral hypoxia as produced by carotid artery compression has shown some promise, and it is the purpose of the present report to record our initial results with this technique. That cerebral function is greatly affected by acute anoxia is not surprising, considering that the brain, although only 2% of the body weight, requires 14% of the total cardiac output and uses approximately 22% of the total oxygen consumption of the body.[1]

Numerous workers * have shown that cerebral hypoxia may be reflected in changes of the electroencephalogram. Engel and Romano [10] observed that the EEG improved when 100% oxygen was given to delirious patients with either heart or pulmonary failure, Cheyne-Stokes respiration, or anemia. Similarly, the EEG of patients with severe anemia was found to improve after blood transfusion. Engel, Webb, and Ferris [11] reported the significant changes in frequency distribution which occur at altitudes of 10,000 ft. (3,000 meters) and progressively increase at higher altitudes.

There are several reports in the literature concerning EEG changes after carotid artery ligation.† Digital occlusion of the ipsilateral carotid artery in a case of carotid-cavernous aneurysm [14] produced loss of consciousness, contralateral Jacksonian seizures, and marked delta activity over the ipsilateral hemisphere 8 to 10 seconds after the occlusion; incomplete compression and carotid sinus massage produced no changes. Carotid compression repeatedly applied during a six-month period continued to give the same results.

From the Department of Neurology, University of California School of Medicine, and the Electroencephalographic Laboratory, University of California Hospital.

* References 2 through 9.

† References 12 and 13.

In the present study the effects of carotid artery compression and carotid sinus massage on the brain waves were investigated. These two maneuvers were performed on 60 unselected patients whose electroencephalograms had been requested for diagnostic purposes. There were 33 males and 27 females. As controls, 10 healthy subjects were tested in the same manner. In no case had carotid compression been performed prior to the EEG recording; thus, any abnormal reaction was first noticed while the experiment was in progress.

METHOD

Standard 18-electrode placements were used except for omission of two frontal leads. These were placed over the precordium for simultaneous electrocardiographic recording. The procedure was performed on 37 patients in the supine, and 23 in the sitting, position. The initial phase of each test consisted of vigorous digital massage of each carotid sinus separately for a minimum of one minute with simultaneous EEG recording. Digital compression of each common carotid artery below the sinus was then performed under the same conditions. The procedure was repeated during both scalp-to-ear and scalp-to-scalp recording from different cortical areas. Each patient underwent a minimum of six separate carotid sinus massage tests and six separate carotid artery compressions. Particular care was taken to determine the location of the carotid sinus at the bifurcation of the common carotid artery. This was usually found to be near the upper border of the thyroid cartilage. Compression of the artery was always carried out at least 3 cm. proximally, i. e., well below the sinus. Frequently the location of the sinus was verified by the appearance of slowing in the EKG during sinus massage. By contrast, the location of the artery below the sinus was made evident by acceleration of the EKG during arterial occlusion.

RESULTS

Of the 60 unselected patients tested, 15 (25%) showed marked EEG changes on unilateral compression of the carotid artery below the sinus. None of the 10 normal controls showed any response to carotid occlusion. Six of the 15 "positive reactors" also showed EEG changes during carotid sinus massage. Marked slowing of the EKG indicated the presence of a sensitive carotid sinus of the vagal type in these six patients. Carotid artery compression in the same cases produced acceleration of the EKG, suggesting that arterial occlusion, well below the sinus, was responsible for the EEG changes, as was the case in the other nine without sensitive carotid sinuses.

The electroencephalographic abnormalities which occurred during occlusion were essentially similar in all cases. They consisted of a rather abrupt appearance of high-voltage slow waves, 2 to 5 per second in frequency, associated with marked irregularity of form and with bilateral asynchrony (Fig. 1). These changes were predominant in the ipsilateral hemisphere and invariably coincided with such clinical manifestations as contralateral dysesthesias and Jacksonian seizures, when the latter occurred, as was frequently the case (Fig. 2). About one-half of the positive reactors lost consciousness during the procedure, while the EEG changes remained predominantly ipsilateral.

The interval between onset of arterial compression and appearance of EEG abnormalities varied in different cases but remained constant for the same patient at different times. The majority of patients who developed such changes did so within from 10 to 20 seconds after the arterial occlusion. The EEG abnormalities invariably preceded the clinical manifestations by a few seconds. Under continued arterial compression the electrical and clinical changes gradually subsided and returned to the precompression state in several cases, suggesting a cerebral compen-

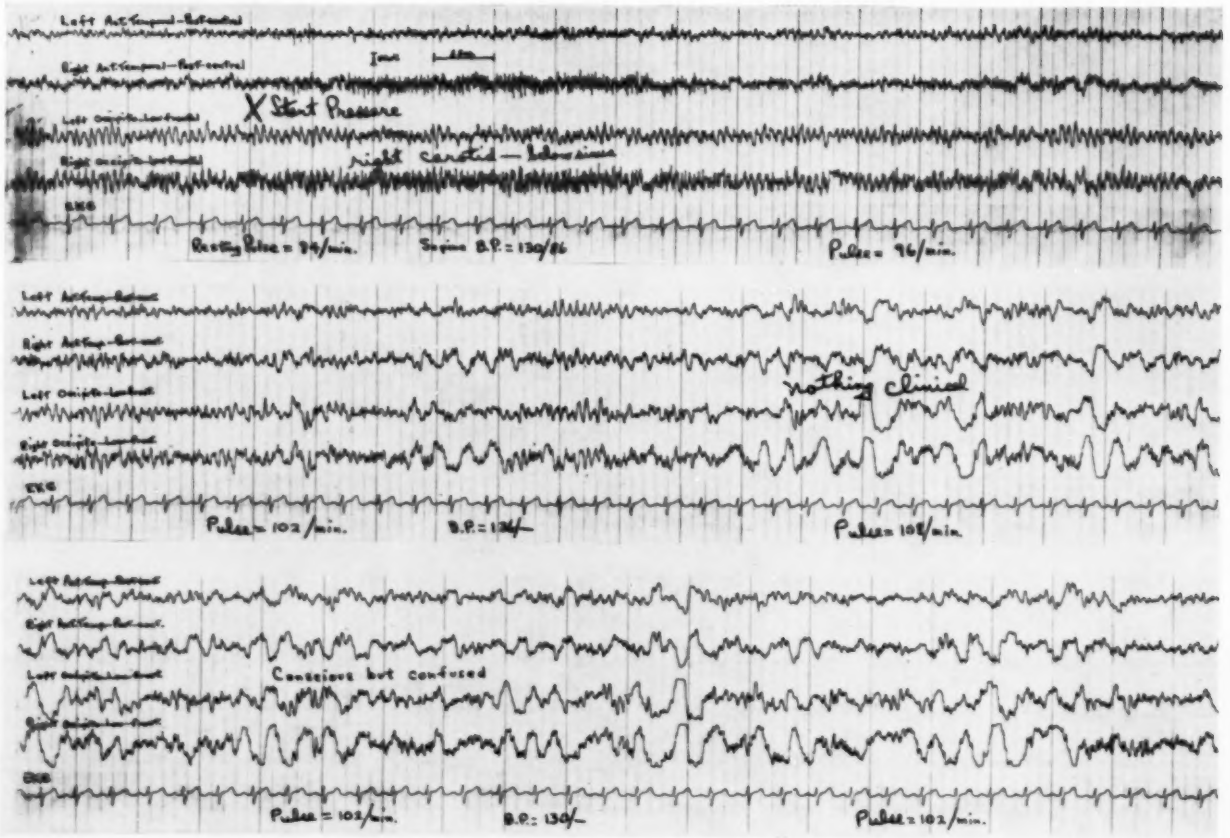

Fig. 1.—Continuous recording during digital compression of right common carotid artery on 57-year-old man with left internal carotid artery thrombosis.

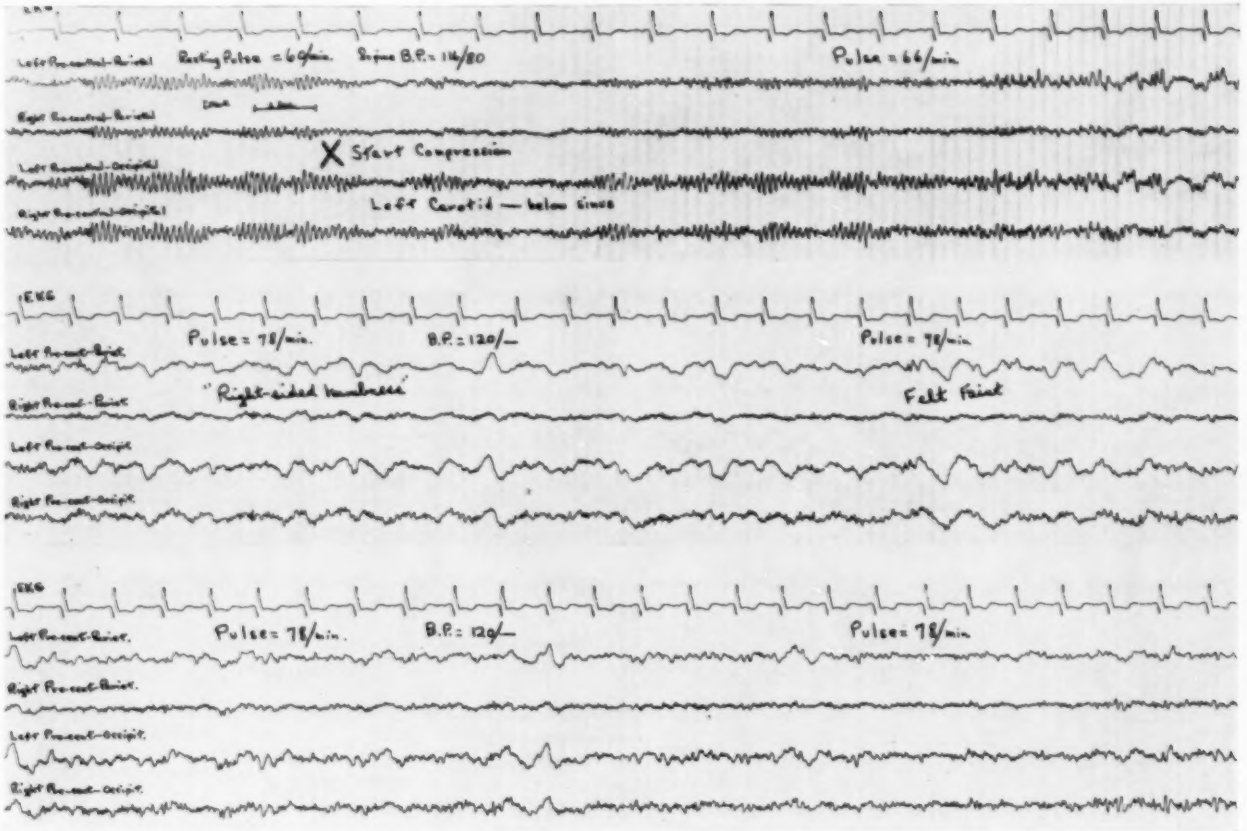

Fig. 2.—Continuous recording during digital compression of left common carotid artery on 61-year-old woman with "cerebral sclerosis" showing predominantly ipsilateral changes, which gradually improve.

satory mechanism, presumably due to an adequate collateral circulation, since the changes persisted for only a matter of a minute or less. This was also suggested by the fact that both the clinical and the EEG responses in all cases remained unchanged on repeated testing. In one case, isolated high-voltage spiking potentials were seen in the left precentral area during the test, that area having shown focal changes but no spiking during the regular EEG.

Eleven females and 4 males exhibited abnormal responses to carotid compression; 16 females and 29 males showed no response. Abnormal, i. e., positive, responses occurred in 12 patients in the supine, and in 3 patients in the sitting, position, while 25 patients in the supine, and 20 in the sitting, position showed no response to arterial occlusion. The average age of the positive reactors was 48 years (range, 14 to 65 years); that of the "negative" ones, 33 years (range, 4 to 68 years). Of the positive reactors, 86% were over 40 years of age, but only 36% of the negative ones were in this age group (Fig. 3). The average age of the healthy controls was 34 (range, 24 to 58 years).

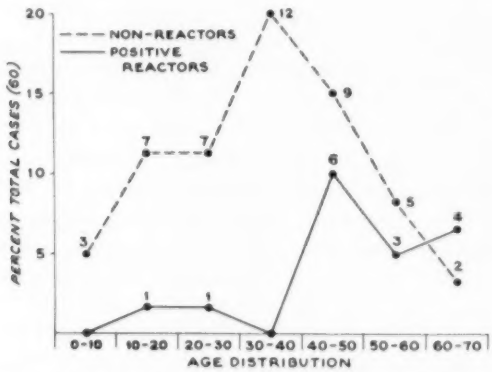

Fig. 3.—Age distribution of positive reactors and nonreactors to carotid artery compression.

Eleven (73%) of the 15 positive reactors had a clinical diagnosis of some form of cerebrovascular disease. Seven of these were diagnosed as "cerebral thrombosis"; four as "cerebral sclerosis." Two of the remaining four had multiple sclerosis, and two had idiopathic convulsive disorders. The clinical diagnoses in the nonreactor group were fairly evenly distributed, with no significant increase of incidence of any single entity (Table). Of the total 60 patients tested, 18 (30%) had a diagnosis of "cerebrovascular disease," and 11 (61%) of these were positive reactors to carotid artery compression.

Cerebral arteriograms were obtained in seven of the positive reactors, five (71%) of whom showed thrombosis of the internal carotid artery. Eleven of the nonreactors had arteriograms; two (18%) of these revealed thrombosis, one with internal carotid, and the other with middle cerebral artery, involvement. Thus, cerebral artery thrombosis was conclusively demonstrated in 33% of the 15 positive reactors and in 4% of the 45 nonreactors.

Six of the positive reactors had pneumoencephalograms; 3 (50%) of these showed cerebral atrophy, as compared with 8 cases of atrophy in 18 air studies

(44%) in the group with no response to carotid compression. Each of the former had proved carotid thrombosis, while the atrophy of the latter was unexplained.

All the cases with a positive response had abnormal pretest electroencephalograms, 33% with generalized changes only, 21% with focal changes only, and 46% with both focal and generalized changes. Of the 45 nonreactors, the regular EEG revealed 27% normal, 9% with general changes only, 18% with focal changes only, and 46% with combined focal and generalized changes. Each of the 10 controls had a normal record.

Clinical Diagnoses of Positive Reactors and Nonreactors to Carotid Artery Compression

	Positive Reactors		Nonreactors		Total	
Clinical Diagnosis	No. Cases	Classified	No. Cases	Classified	No. Cases	Classified
Cerebrovascular	11	..	7	..	18	..
Arteriosclerosis	..	4	..	4	..	8
Thrombosis	..	7	..	2	..	9
Embolism	..	0	..	1*	..	1
Idiopathic cerebral atrophy	0	..	8	..	8	..
Brain tumor	0	..	4	..	4	..
Suspected	..	..	..	3	..	3
Proven	..	..	..	1†	..	1
Idiopathic epilepsy	2	..	12	..	14	..
Grand mal	..	1	..	9	..	10
Petit mal	..	1	..	2	..	3
Temporal lobe	..	0	..	1	..	1
Multiple sclerosis	2	..	2	..	4	..
With cerebral manifestations	..	2	..	0	..	2
No cerebral manifestations	..	0	..	2	..	2
Psychoneurosis	0	..	7	..	7	..
Others, with no cerebral manifestations	0	..	5	..	5	..
Myasthenia gravis	..	..	..	1	..	1
Dermatomyositis	..	..	..	1	..	1
Cervical cord disk	..	..	..	1	..	1
Essential hypertension	..	..	..	1	..	1
Postural hypotension	..	..	..	1	..	1
	15	..	45	..	60	..
Healthy controls	0	..	10	..	10	..
Total	15	..	55	..	70	..

* Rheumatic endocarditis.
† Parietal meningioma.

COMMENT

In order to evaluate the effects of temporary carotid occlusion on the electroencephalogram, a thorough understanding of carotid sinus mechanisms was mandatory as the first step. The vagal, depressor, and cerebral types of carotid sinus syncope have been well established by a number of investigators.‡ Engel and co-workers § studied the EEG changes in patients with sensitive carotid sinus; in their cases occlusion of the carotid arteries below the sinus for 30 seconds produced no clinical or EEG changes. Even with simultaneous occlusion of both carotid arteries for 10 seconds, the EEG changes were only slight. The present work indicates, however, that in certain cases activation of the EEG can be accomplished by unilateral carotid artery compression and that this is unrelated to stimulation of the

‡ References 15 through 27.

§ References 28 and 29.

carotid sinus. A possible mechanism of such changes is the occurrence of cerebral hypoxia resulting from occlusion of the common carotid artery in a person with poor collateral circulation via the circle of Willis. There is some experimental and pathological evidence || to support this hypothesis, and the detrimental effects of anoxemia on the cerebral cortex ¶ are well known. The high incidence of internal carotid artery thrombosis in the present series also favors the view of impaired collateral circulation. In such cases the EEG changes invariably occurred during compression of the artery on the nonaffected side, the artery on the affected side being occluded by thrombosis. Under these conditions the blood supply from the vertebral arteries may well be insufficient, particularly in patients with an anomalous or arteriosclerotic circle of Willis. The higher age of the "positive" cases also parallels the increased incidence of arteriosclerosis.

The significance of the sympathetic nerve supply for the production of cerebral vasomotor changes remains undetermined, although many studies have been performed in this regard.# The changes reported here are not likely to have resulted from stimulation of the cervical sympathetic nerves. There is some evidence [50] to suggest that localized subcortical areas for the regulation of the conscious state may be activated by direct reflex action, by localized vasoconstriction, or by anoxemia. Although the results obtained in the present study conceivably could be explained by such a mechanism, substantiation of this theory is obviously dependent upon focal cerebral blood flow studies, which are not yet available.

This relatively small series does not allow the formulation of any definite conclusions, although the evidence is sufficient to encourage further investigation. The results suggest that a positive EEG response to unilateral compression of the common carotid artery may serve to indicate cerebrovascular insufficiency, an entity which has been thoroughly investigated by Corday and associates.[51] Cases of carotid artery thrombosis, though not uncommon, are said to remain often undiagnosed.* It is in such cases that we have seen a frequent positive response to contralateral compression; here the test may be of special diagnostic value. Again, the procedure may be of value in assessing collateral cerebrovascular circulation, either prior to carotid artery ligation or otherwise, in the study of abnormalities of the cerebrovascular system.

SUMMARY

1. Temporary digital compression of the common carotid artery below the carotid sinus during EEG recording was performed in 60 unselected cases and 10 normal controls.

2. Fifteen (25%) patients showed marked EEG abnormalities, predominantly over the ipsilateral hemisphere. These findings were unrelated to carotid sinus stimulation.

3. Eleven (73%) of the patients showing an abnormal response were clinically diagnosed as "cerebrovascular disease." Five out of the seven (71%) cerebral arteriograms performed in this group revealed internal carotid thrombosis.

|| References 30 through 32.

¶ References 33 through 40.

References 41 through 49.

* References 52 and 53.

4. The evidence, though limited, suggests that carotid compression in certain cases causes EEG changes which might be of aid in the diagnosis of cerebrovascular disease, especially carotid artery thrombosis, and in the evaluation of collateral cerebrovascular circulation, when the adequacy of the latter is suspected or is to be further impaired by carotid ligation.

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Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

Douglas N. Buchanan, M.D., *President*

Leo A. Kaplan, M.D., *Secretary*

Regular Meeting, Nov. 10, 1953

Postmeningitic Hydrocephalus: Case Report. DR. HAROLD C. VORIS, M. D.

A case of postmeningitic hydrocephalus was presented in which the cerebral ventricles had been satisfactorily drained by a ventriculoantral shunt (Nosik). However, the cerebral subarachnoid spaces became greatly dilated. The total protein content of the lumbar subarachnoid fluid was 290 mg. per cubic millimeter, that of cerebral subarachnoid fluid was 173 mg. per cubic millimeter, and that of the ventricular fluid 13 mg. per cubic millimeter. A dye test demonstrated a lack of communication between the cerebral subarachnoid spaces and the lumbar subarachnoid space.

At necropsy inflammatory adhesions of the leptomeninges, especially about the fourth ventricle and brain stem, were demonstrated. The different protein values of the fluids from the lumbar subarachnoid space, the cerebral subarachnoid space, and the cerebral ventricles can best be explained by the dual origin of the cerebrospinal fluid, first proposed by Weed, that is, both from the choroid plexus of the ventricle by a filtration process and from the tissue spaces of the brain by drainage through the perivascular channels into the cerebrospinal fluid spaces, especially the subarachnoid.

The paper will be published in full elsewhere.

Myasthenia Gravis in a Patient with Pseudohypertrophic Muscular Dystrophy. DR. HERMAN CHOR and DR. BENJAMIN H. KESERT.

The case is that of a 62-year-old white man who had the classic picture of pseudohypertrophic muscular dystrophy, which had existed since childhood. There was marked wasting of the muscles of the shoulder girdle, arms, and chest, with pseudohypertrophy of the lower extremities. Recently, following an acute illness called by the patient a "touch of the flu," there was drooping of the eyelids, complete external ophthalmoplegia, and bilateral facial weakness with difficulty in chewing and swallowing. These later symptoms varied from time to time and were worse in the late afternoon hours. Neostigmine (Prostigmin) given intramuscularly produced a prompt and obvious improvement in the muscle power, which constituted a positive test for myasthenia gravis. Upon his being placed on a regime of oral neostigmine therapy, the improvement continued and was apparently sustained. However, on Aug. 16 the patient suddenly had a respiratory crisis and died.

Laboratory and special tests supported the diagnosis of myasthenia gravis superimposed upon pseudohypertrophic muscular dystrophy.

DISCUSSION

DR. ALEX J. ARIEFF: From the standpoint of age the case is interesting; he is an older person. I had a patient who developed myasthenia gravis at 72 years of age. He complains he does not get around as well as before, though he works daily. I wonder how often these two illnesses, myasthenia gravis and muscular dystrophy, occur. I know that Parkinson's disease has been seen with myasthenia gravis, and the other way around. What about the possibility of the so-called "flu" infection starting the syndrome? This man did have an infection which started something that looked like myasthenia gravis.

I wonder if there was some error in the dose of neostigmine which this man was given?

DR. RICHARD RICHTER: I am more struck by the age of the patient in relation to the pseudohypertrophic muscular dystrophy than in respect to the myasthenia. The onset of

myasthenia gravis in the 60's and 70's is no great rarity. I recall, many years ago, telling Dr. Peter Bassoe with much elation my discovery of a patient whose myasthenia had come at the age of 70. He at once topped this by saying that he had seen one begun as late as 85. Some forms of dystrophy, especially partial dystrophy, may persist, or even begin, at a fairly advanced age but it is most unusual in my experience to find a true pseudohypertrophic dystrophy, type Duchenne, in a patient surviving so long.

DR. DOUGLAS BUCHANAN: Is it possible that this patient had myasthenia gravis all his life, and not muscular dystrophy with myasthenia gravis in the later years?

I would agree with Dr. Richter that it is more remarkable to see a man of 65 with muscular dystrophy which started at 12 than to see a man of 65 with myasthenia gravis.

DR. HERMAN CHOR: In our experience the occurrence of myasthenia gravis in conjunction with pseudohypertrophic muscular dystrophy is unique; consequently we thought it would be interesting to our Neurological Society. No doubt some of the members may have seen myasthenia gravis in conjunction with some other neurological diseases. At the present time, I have under study a patient who has myasthenia gravis superimposed on multiple sclerosis. This combination has been reported in the literature.

I agree with Dr. Arieff that the usual dose of neostigmine methylsulfate for diagnostic test is 1 ampule, which contains 1 mg. of the drug. On occasion, I have found this dose too small; therefore we gave our patient three times this dose on testing, and when he was presented before the staff, we administered 6 ampules, with striking results.

The fact that the myasthenic symptoms came on after the occurrence of some type of infection naturally made us consider the possibility that the cells of the nuclei of the cranial motor nerves might have been involved as a form of neuronitis and bulbar palsy. In such an infectious type of paralysis it is very unlikely that the degree of paralysis would vary from hour to hour and from day to day, as occurred with our patient. Furthermore, electrodiagnostic studies and electromyographic tracings showed that there was no involvement of the lower motor neuron.

Although our patient is 62 years of age, the history shows that the muscular dystrophy began in childhood. I am sure that most of us have seen patients who have shown this progressive muscular disorder well into their 50's and 60's. In the Hines Veterans Administration Hospital we have seen many elderly people with muscular dystrophy of long standing. I do not think that a patient would have myasthenia gravis over such a long period of time without its being diagnosed and treated by some physician, or without the patient suffering from some crisis as the result of intercurrent infection or some other malady. Also, we know that myasthenia gravis may have its onset in the later decades, even though it is commoner earlier.

I appreciate the discussion and would like to hear from any members who have encountered patients with myasthenia gravis superimposed on other neurological disorders, inasmuch as I am making a special study of this problem.

DR. IRVING SHERMAN: I saw one patient, a woman of 76, with chorea and myasthenia gravis. She had had the chorea for a number of years and the myasthenia gravis for a few years.

Cytochemical and Cinematographic Analysis of Skeletal Muscle Contraction. DR. JOHN W. HARMAN, Madison, Wis.

Separation of the components of skeletal muscle into pure suspensions of myofibrils, mitochondria, and sarcosomes is accomplished by homogenization and differential centrifugation. Integrated oxidative activity by the Kreb cycle is predominantly in mitochondria, is slight in sarcosomes, and is absent from myofibrils. Admixture of the sarcosomes with mitochondria induces a considerable augmentation of oxidation. The interrelationship of these particles and myofibrils is further studied in whole homogenates in which oxidative activity, mitochondrial morphology, and the structure and contractility of myofibrils are simultaneously assessed. The phases of myofibrillar contraction are minutely studied cinematographically by phase microscopy. The maintenance of myofibrillar structure and contractility is associated with preservation of both mitochondrial form and oxidation. Interaction between the mitochondria and the myofibrils depends on oxidative phosphorylation. Both mitochondria and myofibrils are protected by fluoride, which suppresses with adenosinetriphosphatase and safeguards phosphorylation. Dinitrophenol, which uncouples phosphorylation and oxidation, produces a rapid degeneration of mitochondria and of myofibrils without depressing oxidation. Among

other enzymes, calcium-activated adenosinetriphosphatase and adenylic acid deaminase are located in the myofibrillae with $Q_P(N)$ of 11,000 and $Q_{Sm}(N)$ of 11,600, respectively. Magnesium-activated adenosinetriphosphatase and myokinase are found in mitochondria, where the former has a $Q_P(N)$ of 21,000. Creatine transphosphorylase is located in the sarcoplasm and is obtained entirely in the supernatant fluid free of particles. The sarcosomes (distinct from the mitochondria) are not conclusively associated with any enzymes as yet.

DISCUSSION

DR. JOHN W. HARMAN: I have followed Dr. Gerard's work with much interest. We have recently been examining other organ systems, and we have been able to reverse the state of adenosinetriphosphatase by taking the rod forms and connecting them into the spherical forms, when there occurs a tremendous adenosinetriphosphatase activity, which accompanies oxygen activity. Then by putting them back into reverse again with hyperosmosis, we reduced both the adenosinetriphosphatase activity and the oxidation. We presumed there was a considerable degree of reversibility. I think it has nothing to do with certain membranes, however.

As far as application of currents is concerned, we have not done that. We have been under advice by our physiology department to do this, but we have desisted as yet.

The question of contractures is really one of a degenerative change, because it is a final change. We did not follow it to the stage at which it becomes granular and irregular and noncontractile again. That agrees with Hansen's work.

As for the question of this being a working hypothesis, it is. Krebs has done work which indicates a tremendous building up of adenosine triphosphate. We may be perpetuating the Marsh factor, which is apparently some protein which interferes with the energy system between the myofibril and mitochondria. Marsh uses the state of contraction of the myofibril as a demonstration that adenosine triphosphate is being broken down. But his theory is not clear to me; so I do not know what the situation is. It is not a question of splitting the adenosine triphosphate alone; there is another factor which interferes with the use of adenosine triphosphate.

The final point, the behavior of the myofibril, cannot be explained in terms of membrane, because isolated myofibrils do not have membranes.

Sturge-Weber-Dimitri Syndrome. DR. BEN W. LICHTENSTEIN.

This paper appears in the present issue of the ARCHIVES, page 291.

Obituaries

JOSEPH H. GLOBUS, M.D.
1885-1952

Joseph H. Globus was born on Nov. 25, 1885, in Vitebsk, Russia, and died on Nov. 19, 1952, in New York. Of his almost 67 years, more than half were spent in an extraordinary and single-minded devotion to the problems of the central nervous system, culminating in an impressive work of major significance.

Dr. Globus emigrated to the United States in 1905. Despite almost insuperable economic obstacles, he immediately set out to complete his formal education with a medical career in prospect. In 1915 he received his bachelor's degree from Columbia University and in 1917 his degree of Doctor of Medicine at Cornell. The early years of his medical training were singularly content and productive. Coming under the wing of Stockard, his early interests were focused on neuroanatomy, and he initially felt content to devote most of his attention to scholarly work in this field. Despite deviations from this course, his anatomical scholarship persisted through the rest of his life and was the core around which he built his other work.

Partially as a result of his residency at the Montefiore Hospital in 1917 and his service in the United States Army Medical Corps in World War I, and as a member of the staff of the Mount Sinai Hospital in New York, his interest began crystallizing in the direction of neuropathology. Starting as a Blumenthal research fellow in 1920, he became an adjunct (1921-1928), an associate (1928-1939), neuropathologist (1939-1951), and consulting neurologist and neuropathologist at the time of his retirement. In addition to creating the neuropathology department at Mount Sinai, his laboratory became one of the major research and teaching centers in this field under his aegis. His department educated numerous students and produced a wealth of work, all characterized by a pattern of scholarship which became synonymous with his name.

The quality of Dr. Globus' research is well known. The study of brain tumor is radically incomplete without reference to his many contributions, ranging from theories as to the origin of brain tumors to a system of classification which was defended and reiterated by him in his last paper, which has just recently been published. His original works on spongioblastoma multiforme, infundibuloma, amaurotic family idiocy, and massive cerebral hemorrhage are all landmarks.

But, while continuing with original research, he devoted himself wholeheartedly to his great love—teaching. His professorial career began in 1910 at University and Bellevue Hospital Medical College, where he gave his initial course on Neuroanatomy. In 1915 he was teaching at Cornell, and in 1923 he began his long association with New York University, holding the position of associate professor. He also taught clinical neurology at the Columbia University College of Physicians and Surgeons, which appointed him associate clinical professor in 1937. His books, "Aid in the Study of Neuroanatomy" (five editions) and "Practical Neuroanatomy," have given permanence to this life work of teaching and study.

His love of teaching was reflected in other directions. Responsible for the formation of two medical journals, he viewed them as an additional means of presenting the highest scholarship to the widest possible audience. He was editor of the *Journal of Neuropathology and Experimental Neurology* and of the *Journal of the Mount Sinai Hospital*. Despite research, teaching, medical practice, and his formal obligations as an Attending at Mount Sinai Hospital, he still found time for the almost single-handed and Herculean task of editing both these journals.

There were many honors bestowed upon him. The Howe Medal was awarded to him by the University of Buffalo School of Medicine as a member of the American Anatomical Society (1915); the presidency of the Section of Neurology and Psychiatry of the New York Academy of Medicine; the presidency of the American Association of Neuropathologists (1942), and the citation as "Man of the Year" by the Mount Sinai Alumni Association (1951). He was a member (1923) of the American Neurological Association and became a senior member in 1950.

There were many opportunities to change the course and pattern of his life. Harvey Cushing asked Dr. Globus to join him; he was offered major teaching appointments in other schools; his practice in neurology and psychiatry might have expanded considerably. But he began this career as an independent and rigorously honest scholar, and this was the way he chose to end it.

As a human being he gave himself unsparingly to his patients, his friends, his students. Witty, acute, and learned, he was an astute conversationalist. His wife and three children were always closest to his heart and his thirty years of married life were marked by great personal happiness. Honest and outspoken, he was at times a controversial figure. But always and unfailingly he followed the straight path of creative research and teaching.

ARTHUR WEIL, M.D.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

EXPERIMENTAL RADIO-NECROSIS OF THE BRAIN IN RABBITS. D. S. RUSSELL, C. W. WILSON, and K. TANSLEY, J. Neurol., Neurosurg. & Psychiat. **12**:187 (Aug.) 1949.

Russell and her associates attempted to reproduce experimentally the lesions previously reported in human subjects following therapeutic irradiation of the central nervous system. For this purpose, four groups of rabbits were given single doses of x-rays directed to the left side of the skull. Group 1 comprised animals which received 2,850 r; group 2, five animals which received 2,440 r; group 3, two animals which received 2,030 r, and group 4, two animals which received 1,625 r. The animals were killed at various periods before, during, and after the onset of neurological symptoms. In groups 1 and 2, "presymptomatic" and "postsymptomatic" periods were described, while the animals of groups 3 and 4 remained entirely asymptomatic. The authors found that in group 1 a single dose of 2,850 r produced radiation necrosis in the rabbit's brain after a latent period of approximately 100 days. In group 2, in which the dose was reduced to 2,440 r, the same changes were noted, but the latent period was more than doubled. Since the animals in groups 3 and 4 showed no abnormalities, it was concluded that the minimal dose which would produce radiation necrosis lay between 2,440 and 2,030 r. The earliest histological changes consisted of minute foci of hemorrhage and necrosis intimately related to perforated vessels, particularly capillaries, but there were no alterations in the walls of these vessels. In later stages the lesions were characterized by pronounced gliosis and by progressive degeneration and sclerosis of adjacent vessels. The lesions affected the deeper parts of the cerebrum, the meninges, and the superficial parts of the cerebrum escaping, except for the cerebellum, the cortex of which bore the main brunt. Thus, in contrast with human material, there was no definite proof that radiation necrosis had a vascular pathogenesis.

N. MALAMUD, San Francisco.

LIPOLYTIC ACTIVITY OF THE SPINAL FLUID IN NEUROSYPHILIS. G. G. GIORDANO and P. SALVI, Acta neurol. **6**:665, 1951.

Giordano and Salvi found that the lipolytic activity of the spinal fluid was slightly higher in patients with neurosyphilis than in normal persons. Whereas the mean of the lipolytic activity was 1.40 ± 0.60 cc. of 0.01 N NaOH in the normal, it was 1.50 ± 0.82 cc. of 0.001 N NaOH with neurosyphilis patients. The increase was particularly marked in the fluids in which the protein content was also increased. The authors feel that the increased lipolytic power is due not to an increase in the enzymes, but to an increased amount of substances which activate the enzymes themselves.

ARIETI, New York.

Psychiatry and Psychopathology

THE MEANING OF DÉJÀ VU. ELI MARCOVITZ, Psychoanalyt. Quart. **21**:481 (Oct.) 1952.

Marcovitz believes that the feeling in déjà vu, "I have experienced all of this just this way before," is better understood if it is thought of as *encore vu:* "I am experiencing all this again; I am having a second chance." It is an illusory fulfillment of a wish that one could repeat some previous experience so that one could make the outcome accord better with a desire: "If it be true that I am re-experiencing this, then I can hope that I will have a second chance to realize some other more important unfulfilled wish." Latent déjà vu wishes occur at various levels of awareness; some are readily available to consciousness; others, more primitive, are deeply depressed.

WERMUTH, Philadelphia.

OBSERVATIONS ON INSULIN SUBSHOCK TREATMENT IN A VETERANS ADMINISTRATION MENTAL HYGIENE CLINIC. K. NUSSBAUM, H. GOLDSMITH, and E. C. HENRY, Psychiat. Quart. **25**:641 (Oct.) 1951.

The authors deal with observations on physiologic and psychologic reactions in patients undergoing subshock insulin treatment in a mental hygiene clinic. An attempt is made to show the value of such treatment as an adjunct to psychotherapy and to describe some important points in nursing technique peculiar to an outpatient clinic not directly connected with a hospital. All patients were ambulatory, and most were working or attending schools. An outpatient clinic has very little control over the activities of insulin patients before or after treatment and is very much dependent on the active cooperation of the patients. This in itself is considered an important psychotherapeutic factor and incentive to the patients.

Criteria for the selection of suitable patients are (*a*) a history of previous successful treatment course, (*b*) loss of weight, (*c*) tension and anxiety with or without autonomic manifestations, (*d*) neurasthenic complaints, (*e*) inaccessibility to psychotherapy in withdrawn and schizoid persons, and (*f*) affective deprivation and lack of group contact.

The authors (*a*) recommend rest at the end of each treatment; (*b*) questioning of the patient prior to each treatment regarding food intake, fatigue, intercurrent illnesses, and emotional factors, in order to avoid untoward reactions, and (*c*) particular caution in the case of alcoholic patients. The authors discuss warning signs for termination of subshock and describe psychotic reactions under insulin and their effect on other patients.

It has been found necessary to prevent such untoward reactions as much as possible by controlling the insulin dose and the length of each individual treatment. Any loss of physiologic benefits due to insulin is amply compensated for by the continued positive motivation of the patients for the treatment.

Some of the psychotherapeutic effects of insulin subshock in this mental hygiene clinic seem to be caused by an emotional group experience. Psychotherapy is necessary in conjunction with ambulatory insulin treatment. The individual needs of each patient must be considered in planning his treatment. The psychiatric nurse makes an important contribution to the program, particularly in dealing with patients of the more dependent type.

The writers conclude that insulin subshock treatment in an outpatient clinic on a more extensive basis is not only feasible but desirable.

FROM THE AUTHORS' ABSTRACT.

Meninges and Blood Vessels

RECURRENT EXTRADURAL CEREBELLAR HEMATOMA. E. L. GAGE, Am. J. Dis. Child. **84**:82 (July) 1952.

The patient, a 6-year-old girl, fell from her bed to the floor, striking her head. Shortly after this she began to complain of headache and the following day was nauseated, vomited, and was restless. When she was admitted to the hospital, two days later, there was evidence of increased intracranial pressure. A roentgenogram of the skull revealed a questionable subperiosteal fracture in the left occipital region.

Bilateral upper occipital burr holes were made, and when no extradural or subdural clot was encountered, a ventriculogram was done via the right ventricle. The ventricles were shown to be in their normal positions, with air in each side. After the ventriculogram, the child brightened, but 48 hours later she again showed signs of increasing intracranial pressure. On the fifth day after the injury, a midline suboccipital approach was made to the posterior fossa, and an extradural hemorrhage of the left posterior fossa was evacuated. A careful search was made for a bleeding point, but none was found.

The patient did well for three days, when there was again evidence of increasing intracranial pressure, with bilateral papilledema and internal squint. Again the posterior fossa was exposed and the bone removed widely, as for a classic suboccipital craniotomy. There was a second accumulation of clot on the left, apparently coming from a small leak in the lateral sinus, which

had not been found before. The dura was opened, the cerebellar tonsils freed, and the aqueduct exposed after evacuating the second clot to insure complete relief of compression from the clot and to help reestablishment of the spinal fluid circulation.

The patient made an uneventful recovery and a five-year follow-up study indicated satisfactory rehabilitation.

ALPERS, Philadelphia.

SYNCOPE, VERTIGO AND DISTURBANCES OF VISION RESULTING FROM INTERMITTENT OBSTRUCTION OF THE VERTEBRAL ARTERIES DUE TO DEFECT IN THE ODONTOID PROCESS AND EXCESSIVE MOBILITY OF THE SECOND CERVICAL VERTEBRA. F. R. FORD, Bull. Johns Hopkins Hosp. **91**:168 (Sept.) 1952.

This paper describes a very unusual case history. It is that of a youth of 17 years who was subject to attacks of syncope, which were followed by nystagmus, diplopia, blurring of vision, and unsteadiness. It was found that the odontoid process was missing and that excessive mobility of the second cervical vertebra was present. It was not decided whether this defect in the odontoid process was a result of injury or a defect of development. Immobilization of the neck by a plaster cast, and later by operative fusion, gave complete relief of the symptoms.

Ford presents evidence to show that displacement of the axis led to transient obstruction of the vertebral arteries and that interruption of the circulation of the brain stem was responsible for the symptoms.

He suggests that this condition, i. e., obstruction of the vertebral arteries, may occur in cases of fracture or dislocation of the cervical portion of the spine.

ALPERS, Philadelphia.

TRAUMATIC INTERNAL CAROTID ARTERY THROMBOSIS SECONDARY TO NONPENETRATING INJURIES TO THE NECK. R. C. SCHNEIDER, and L. J. LEMMEN, J. Neurosurg. **9**:495 (Sept.) 1952.

Schneider and Lemmen state that traumatic internal carotid artery thrombosis secondary to nonpenetrating injuries to the neck should be considered in the differential diagnosis of craniocerebral trauma. They review five cases of concomitant head injury and traumatic internal carotid artery thrombosis of this type found in the literature and report two similar cases of internal carotid artery thrombosis which occurred secondary to nonpenetrating injuries to the neck and simulated epidural or subdural hematoma.

In patients who present clinical signs and symptoms simulating those of acute head injuries the diagnosis of thrombosis of the internal carotid artery may be suspected when a combination of neurologic signs and trauma to the neck is observed. In the majority of cases of acute thrombosis of the internal carotid artery the signs and symptoms may develop within a period of 6 to 24 hours, as contrasted with the longer interval for spontaneous thrombosis. The clinical manifestations of these lesions depend on several factors: (1) the extent of the thrombosis, (2) the competence of circulation in the circle of Willis, (3) the presence of vasospasm, (4) the presence of the lesion in the dominant or minor hemisphere, (5) the severity of associated craniocerebral injury, and (6) the degree of secondary hypoxia. These may result in alterations in the state of consciousness, hemiplegia, aphasia, blindness, visual field defects, and Horner's syndrome.

If the patient is cooperative, the measurement of the retinal artery pressure by Bailliart's ophthalmodynamometer may give a definite indication of the presence of this lesion. However, angiography presents the most accurate method of diagnosing thrombosis of the internal carotid artery during life.

In treatment, prompt diagnosis, the use of anticoagulant therapy, the increase of blood flow through the collateral channels by cervical blocks or cervical sympathectomy, and the use of papaverine as a supplementary vasodilator are indicated. In those cases in which thrombosis has been extensive and signs of increased pressure and cerebral edema are present, early bilateral subtemporal decompression may be of some benefit in avoiding pressure on the medullary and midbrain centers by prevention of cerebellar and temporal pressures cones.

ALPERS, Philadelphia.

THE OCULAR COMPLICATIONS OF CAROTID ANGIOGRAPHY. F. B. WALSH, and G. W. SMITH, J. Neurosurg. **19**:517 (Sept.) 1952.

This paper is divided into two parts. In the first part the ocular symptomatology associated with the injection of iodopyracet (Diodrast) into the common carotid artery is described, accompanied by illustrative cases. The symptomatology associated with angiography includes pain; retinal irritation; pupillary changes; narrowing of the retinal vessels; hemorrhages in the skin, conjunctiva, and retina; allergic phenomena, and changes in visual acuity. According to the authors, the procedure holds an almost negligible threat as regards permanent loss of vision, and transient loss of vision occurs rarely. So far no case of bilateral loss of vision has been reported as a result of angiography.

In the second part of the paper thrombosis of the internal carotid artery is considered from the standpoint of its ocular symptoms and signs. These may include blindness of the homolateral eye, retinal hemorrhages, pain in the eye, hemianopsia, pupillary changes, ophthalmoplegia, and papilledema. Several cases are included. An observation of importance was described in five cases of hemianopsia. In all there was a tendency toward sparing of the upper quadrant of the defective half-fields. From their studies of the arterial supply to the visual pathways the authors assume that in these cases the principal arterial obstruction occurred in the branch or branches from the middle cerebral artery to the optic radiation. Such a constant finding in the visual fields may have been merely chance, but this possibility seems unlikely. They urge further work on the vascular supply to the visual pathways.

ALPERS, Philadelphia.

CEREBRAL HEMORRHAGE IN HYPERERGIC ANGIITIS. F. HILLER, J. Neuropath. & Exper. Neurol. **12**:24 (Jan.) 1953.

Hiller reports on two patients who succumbed to a massive brain hemorrhage, the one suffering from thromboangiitis obliterans, the other from polyarteritis nodosa. Both these diseases are, as a rule, distinct disease entities from a clinical viewpoint; yet both diseases go through stages of development which show considerable variation in their pathology, as well as their potential clinical manifestations. Acute inflammatory reactions are seen occasionally in the generally insidious course of thromboangiitis obliterans comparable to the acute phases more frequently observed in polyarteritis nodosa. The explanation that both diseases represent hyperergic vascular tissue reactions is well founded and may be accepted as a sound basis for the understanding of the pathogenesis of these diseases.

These two cases demonstrate that brain hemorrhage may occur in the course of thromboangiitis as well as in that of polyarteritis nodosa. Such a hemorrhage can originate, as in one of these cases, on the basis of acute hyperergic phlebitis migrans of the cerebral veins in thromboangiitis, and of an acute or subacute arteritis, possibly with phlebitis, in polyarteritis nodosa. In the chronic stage of this disease massive brain hemorrhage may also occur as hypertensive encephalopathy with the clinical syndrome of a pseudouremia. Hemorrhages from an acute hyperergic angiitis resemble brain hemorrhages seen in toxic encephalopathy, although in this syndrome, generally described under the term brain purpura or hemorrhagic pseudoencephalitis, multiple petechial hemorrhages are more frequent than true massive hemorrhages originating from larger blood vessels. Hiller suggests that the basic difference between hyperergic angiitis and toxic vascular lesions probably lies in the different mode of interaction between vascular tissue and toxic agents.

Sensitization of vascular tissue elements to toxic antigenic substances and consecutive hyperergic tissue reactions determine the vascular lesion in hyperergic angiitis. There the allergic element and the tissue factor appear to be decisive, and there may be various antigenic substances which keep the hyperergic vascular reaction going. In toxic hemorrhagic encephalopathy, on the other hand, the sensitization or affinity of the vascular elements appear to be overshadowed by the extreme toxicity of certain agents. One may expect a more acute course of the disease and less tissue specificity in the toxic than in the true hyperergic group of manifestations. It is possible that hyperergic and predominantly toxic damage to blood vessels are often combined in individual cases, and this may explain their exceptional features.

ALPERS, Philadelphia.

SUGAR CONTENT OF THE CEREBROSPINAL FLUID IN DIFFUSE NEOPLASTIC INVOLVEMENT OF THE MENINGES. H. W. DODGE, JR., G. P. SAYRE, and H. J. SVIEN, Proc. Staff Meet., Mayo Clin. **27**:259 (July 2) 1952.

That depression of the sugar content of the cerebrospinal fluid may be caused by infections of the meninges with pyogenic, tuberculous, fungous, and yeast-like organisms is well known. The fact has been largely overlooked that in the occasional difficult case in which there are signs of poorly localized involvement of the central nervous system a low concentration or absence of sugar in the spinal fluid in the presence of an adequate concentration of blood sugar may indicate carcinomatous, sarcomatous, or gliomatous involvement of the meninges.

The authors describe four such cases in which difficult diagnostic problems were presented and in which sugar was low in concentration or absent from the spinal fluid. At necropsy diffuse meningeal neoplasms were observed. The awareness that a low sugar content of the spinal fluid sometimes occurs in diffuse meningeal neoplasms led to correct a presumptive diagnosis in three of these four cases before death.

The possible causes of the lowering of the sugar content of the cerebrospinal fluid in such cases is discussed. Dodge and his co-workers feel it is possible that more than one mechanism is at work, and that the reduced sugar content of the cerebrospinal fluid in diffuse meningeal neoplastic involvement is due not only to an accelerated cellular metabolism but also to a simple mechanical blocking.

When there is little or no sugar in the spinal fluid in a confused and difficult diagnostic problem, the clinician may well consider the possibility of diffuse neoplastic involvement in his diagnostic differential, even in the absence of a demonstrable primary neoplastic source.

ALPERS, Philadelphia.

Diseases of the Brain

EXOPHTHALMOS DUE TO MUCOCELE OF THE MAXILLARY SINUS. V. CHINAGLIA, Riv. oto-neuro-oftal. **26**:10 (Jan.-Feb.) 1951.

Eight cases have been reported since 1880 in which mucocele of the maxillary sinus extended into the orbit. A man aged 44 complained of diminished vision in the left eye, photophobia, and frontal headache about four months before he was first seen; he also noted prominence of the left eye. Examination revealed exophthalmos of the left eye; the exophthalmometric readings (Hertel) were 19 mm. on the left and 13 mm. on the right. The exophthalmos was not reducible; no bruit was heard, and there was no pulsation of the eyeball. The pupils were equal and regular and reacted to light and in accommodation. The corneal reflexes were equally active; the veins in the left fundus were dilated, the disk edges slightly blurred, and the disk itself was hyperemic. Vision was impaired and was not improved by refraction. There was a central scotoma for color on the left side. The left maxillary, frontal, and ethmoid sinuses appeared cloudy in roentgenograms. The medial wall of the left orbit seemed eroded. At operation an area of erosion, about 2 cm. in diameter, was found in the roof of the maxillary sinus. Pus and serum, evidently coming directly from the infected maxillary sinus, were found in the retro-orbital region. The arteriograms revealed nothing abnormal. Histologic examination of tissue from the maxillary sinus showed polypoid degeneration. There were no clinical signs of infection of the sinus or the orbit.

N. SAVITSKY, New York.

HELLER-ZAPPERT DISEASE (INFANTILE DEMENTIA). D. L. OUTES and A. M. FIERRI, Prensa méd. argent. **40**:458 (Feb. 20) 1953.

Heller, in 1908, and Zappert, in 1921, described a form of dementia in children. The affected children develop normally up to the third or fourth year, when language disorders appear, which are soon followed by mental changes, restlessness, and progressively severe dementia. The children do not usually look like imbeciles or idiots. No neurologic signs were reported. The facial expression remains fairly normal in spite of the deterioration. In 1926, Corberi reported the first anatomic studies in two cases of this type; in both anatomic changes of amaurotic

familial idiocy were apparent. Weygandt, in 1933, reported a case in which degenerative changes were present in ganglion cells of the brain; the degenerative changes noted by Corberi were not found.

The authors report the first case of Heller-Zappert disease (infantile dementia) in Argentina. The boy developed normally until his fourth year. Two months after he was frightened by a barking dog he began to have language difficulties. His speech became progressively worse, and he became very restless and had difficulty in taking care of himself. Some ability to appreciate and to react emotionally to music was conserved. Psychiatric studies, at the age of 12 years, showed utter inability to speak, evident dementia, restlessness, and incoordinated movements of the upper extremities. The affective reactions were defective. The neurologic findings were entirely normal. Spinal fluid studies showed a total protein content of 29 mg. per 100 cells, 3 cells per cubic millimeter, and a negative Wassermann reaction. Pneumoencephalography showed a dilated ventricular system and cortical atrophy.

N. Savitsky, New York.

Diseases of the Spinal Cord

Disorders of Respiration in Bulbar and Other Forms of Poliomyelitis, with Special Reference to Muscle Spasm. J. F. Pohl, Arch. Pediat. **66**:537 (Dec.) 1949.

Pohl reports on 368 patients with poliomyelitis who were admitted to one of the receiving units in Minneapolis during the 1946 epidemic. Forty-three of the 368 patients had respiratory disorders. Death occurred in 18 cases (4.9%). Breathing disorders were present in 16 of the fatal cases and absent in 2. Spasm causes muscle tissue to contract and shorten, and in this way the condition has an effect on respiration. Spasm of the chest muscles was either a serious cause of or a contributing factor in the breathing difficulty in 38 of the 43 patients with true respiratory disorders. Breathing disturbances in poliomyelitis are not confined to patients showing paralysis. Spasm of the intercostal muscles, as well as of the abdominal and spinal muscles, can restrict breathing. Spasm of the pectoral muscle is severely painful and inhibits breathing. Spasm of the diaphragm causes an exhalatory type of difficulty, in which the chest is expanded and the patient's eyes bulge on exhalation, in his attempts to rid the lungs of the air. The best treatment of muscle spasm is application of moist heat. The mechanical respirator aggravates the spasm and makes treatment of the muscles difficult. Every effort should be made to continue treatment of the chest muscles of patients with paralysis in addition to spasm who must be placed in a respirator. It may be possible to open the respirator at hourly intervals throughout the day and apply hot foments to the chest. Paralysis of the chest sufficient to impair respiration was present in 12 of the 43 patients with true breathing disorders. In 10 of the 12 paralytic patients muscle spasm was a factor contributing to the respiratory distress. Chest muscle spasm was associated with bulbar poliomyelitis in 21 of the 73 cases of this type, in many of which spasm of the muscles of the neck was a complication.

J. A. M. A.

Typhoid Spondylitis with Compression of the Thoracic Region of the Cord. B. B. Spota and C. A. Bardeci, Prensa méd. argent. **37**:3035 (Dec. 15) 1950.

A white woman aged 24 was admitted to the hospital on March 10, 1948. During August, 1947, she began to complain of pain in the left side of the chest, radiating to the left arm. The pain was intensified by coughing and sneezing. Toward the end of February, 1948, weakness of the lower limbs appeared. She had typhoid in 1928 and "pleuritis" on the left side during February, 1945.

On her admission to the hospital there was weakness in all muscle groups in the lower extremities, with hyperreflexia and a bilateral Babinski sign, and a sensory level at the second thoracic on the right and the first thoracic on the left. The second thoracic vertebra was tender. Examination of the spinal fluid showed complete block. A roentgenogram of the spine showed intense osteoporosis of the posterior arch of the first thoracic vertebra, especially on the left. The Widal reaction was positive on April 7. Before treatment was begun, there were complete paraplegia, decubitus ulcers in the region of both heels, and edema of both lower limbs. She was given intravenous injections of typhoid vaccine and 120 gm. of streptomycin. On June 6,

1949, she was definitely better, with no weakness in the lower limbs and a negative Widal reaction. Paralysis of the lower extremities began to improve in October, 1948; at the end of November she was able to walk. On June 6, 1949, there was numbness on the right in the first thoracic dermatome; reflexes were hyperactive in the lower limbs, especially on the left. There was evidence of involvement of the posterior column in the lower limbs, particularly on the left, with mild hyperalgesia in the left lower extremity to the root of the limb.

The author believes that changes in the spinal column and cord were due to typhoid, in spite of the long interval between the occurrence of this infection and the onset of the present illness. The compression of the cord was probably due to an epidural abscess. The intense osteoporosis of the whole of the posterior arch is noted as exceptional.

N. Savitsky, New York.

Peripheral and Cranial Nerves

Herniated Intravertebral Disks Which Do Not Account for Pain. C. Gama, Arq. neuro-psiquiat. **8**:243, 1950.

Two cases are reported in which posteriorly displaced disks were seen in myelograms. In each case the myelographic findings and the apparent herniation were coincidental observations. In the first case the patient failed to improve after an operation in which a herniated disk was removed. A neurinoma, accounting for the sciatic pain, was found in the left sciatic nerve. Lobotomy had to be done ultimately for relief of the severe pain. The second case was that of a man aged 62 who complained of pain in the chest and the left lower limb. An operation was not done, though evidence of a disk was present in the myelogram. The patient responded to deep x-ray therapy, the pain disappearing completely in 24 hours. The author believes the pain was due to radiculitis. It seems therefore that herniated disk may occasionally be a coincidental finding and may not account for pain in the back or the lower extremities. The presence of other causes of sciatic pain in patients with defects in the myelogram may account for the occasional failure of operative intervention.

N. Savitsky, New York.

Pathogenic Relation of Ménière Syndrome to Glaucoma. G. Fontana and M. Cristiani, Riv. oto-neuro-oftal. **25**:341 (Sept.-Oct.) 1950.

The case of a woman with a typical Ménière syndrome and glaucoma is reported in detail. Eighty-four cases of Ménière's syndrome and 26 cases of glaucoma were studied. In five cases the two conditions coexisted. Three of the five patients were men and two women, their ages ranging from 40 to 70. In four of these patients the glaucoma followed the Ménière syndrome, and in one the glaucoma appeared first. All five patients had allergic tendencies. The authors conclude that the coexistence of the two conditions is not coincidental but that both probably occur on an allergic basis.

N. Savitsky, New York.

Treatment, Neurosurgery

Treatment of Neurogenic Urinary and Fecal Incontinence in Children. R. E. Gross; G. W. Holcomb Jr., and H. Swan, A. M. A. Arch. Surg. **66**:143, 1953.

In children, the treatment of neurogenic disturbances of the bladder and rectum presents perplexing problems. Urinary and fecal incontinence usually are the result of lumbosacral myelodysplasia, meningomyelocele, or lipoma. Children with these lesions are constantly uncomfortable, wet, and smelly, being soiled by their excretions. Since the skin around the genitalia, perineum, and thighs is apt to become macerated and infected, the nursing problem is most difficult. The authors report their experiences with 21 such cases. Local corrective procedures should be tried only after all means of neurosurgical repair have been exhausted. Below an age of 4 years, mild urinary incontinence may not require surgical treatment but may respond to bladder training. In the "overflow bladder," with excessive sphincter tone, transurethral resection of the bladder neck may be beneficial; occasionally, however, this operation makes the situation worse by causing constant dribbling.

Surgical repair of relaxed anal and rectal sphincters should not be attempted before an age of 5 or 6 years. If only rectal incontinence is present, the combined use of constipating diet and daily cleansing enemas may prove satisfactory; at any rate, colostomy will be of no benefit. In some instances, surgical reduction of the bladder outlet by plication of the bladder wall will successfully overcome the constant dribbling. If the patient has severe incontinence, a so-called wet colostomy is indicated (it discharges both fecal material and urine). The excretions are collected in a colostomy bag, which has to be cemented to the abdominal wall and contains a disposable plastic sac. It is inadvisable to construct a new bladder from the sigmoid. Diversion of the urine from the perineum can be accomplished by interruption of the urethra, closure of the bladder outlet, and establishment of a permanent suprapubic cystotomy. The cystotomy tube may be clamped, provided the urethrovesical valves are competent and renal function is adequate; otherwise, the tube should be left open.

Constant medical supervision of these children is mandatory to prevent complications.

LIST, Grand Rapids, Mich.

PARALYSIS DUE TO REDUCED SERUM POTASSIUM CONCENTRATION DURING TREATMENT OF DIABETIC ACIDOSIS: REPORT OF CASE TREATED WITH 33 GRAMS OF POTASSIUM CHLORIDE INTRAVENOUSLY. F. I. STEPHENS, Ann. Int. Med. **30**:1272 (June) 1949.

The treatment of severe diabetic acidosis has been associated occasionally with profound weakness and eventual paralysis of the muscles of respiration, and it has been demonstrated that this complication is associated with low serum potassium concentration. In such cases the administration of potassium salts has resulted in dramatic improvement.

Stephens reports the case of a white woman aged 28, married, with diabetic acidosis. The patient was treated for her acidosis with zinc insulin crystals and given continuous intravenous infusions. In addition, she was given gastric lavage with 5% sodium bicarbonate solution.

About four hours after her admission the respirations became rapid and shallow, but the sensorium was clear. There was extreme weakness of the muscles of all the limbs and, to a less extent, of the neck muscles. The deep reflexes were absent throughout. The development of this profound muscular weakness suggested the possibility of a low potassium concentration of the serum. The electrocardiogram taken five hours after her admission revealed sagging of the S-T segments and low amplitude of the T-waves in all leads. The serum potassium six hours after admission measured 1.8 mEq. per liter. The electrocardiogram taken at this time showed further changes, and two hours later the potassium was further reduced to 1.4 mEq. per liter and there were even more striking changes in the electrocardiogram. The patient became progressively weaker.

Nine hours after her admission administration of insulin and dextrose was discontinued, and over the subsequent two hours the patient was given intravenously 2,000 cc. of a solution containing 0.4% potassium chloride (54 mEq. of potassium per liter) and 0.6% sodium chloride in distilled water. Potassium citrate, 2 gm., was given orally during the first half-hour. Potassium chloride solution was administered at the rate of 18 to 20 cc. per minute. Definite regression of the electrocardiographic abnormalities was observed within 10 minutes. However, there was no corresponding improvement in the clinical condition of the patient. She complained of numbness and tingling in both hands, and examination revealed flaccid paralysis of both arms and legs. She was unable to raise or turn the head from side to side. Respirations were almost entirely diaphragmatic, with hardly discernible excursions of the chest. Speech, mastication, deglutition, and ocular and facial movements were grossly impaired. The patient was able to move the toes of both feet only slightly. Deep reflexes were unobtainable, and the plantar reflexes were absent. Tactile sensation to pinprick and cotton wool was intact.

Potassium therapy was continued at approximately the same rate, and there occurred a gradual return of muscular power. The paresthesias of the arms slowly subsided, and the electrocardiograms showed gradual progress toward normal. In all the patient had to receive 33 gm. of potassium chloride intravenously. The intravenous therapy was discontinued 24 hours after her admission, at which time the patient was able to move about and feed herself without difficulty. She made an uneventful recovery.

The physiological mechanism responsible for the reduction in serum potassium concentration in such cases is associated with dehydration, which is characteristic of diabetic acidosis, with a resultant loss of both intracellular and extracellular water. Potassium is lost from the cells with water and is excreted in large quantities in the urine. The concentration of potassium in the extracellular fluid, however, remains normal and may be slightly elevated. The administration of insulin produces a reduction in serum potassium concentration in both normal and diabetic persons; along with this, the administration of large amounts of dextrose has a similar effect. This reduction in serum potassium has been shown to be the result of movement of potassium from the extracellular fluid into the tissue cells in the company of glucose—a normal response in increased glycogen formation.

In diabetic acidosis, even after the institution of the usual types of insulin and glucose therapy, some patients continue to excrete large amounts of potassium in the urine. This loss is sufficient to account for the symptoms and necessitates the type of management indicated in this paper.

In the present case an unusually large amount of potassium had to be administered to the patient, and Stephens stresses the importance of anticipating the development of hypokalemia and, when it occurs, of instituting treatment promptly in order to avoid the serious effects of extreme reduction in serum potassium levels. He also advocates the use of the electrocardiogram as a rapid and convenient means of detecting reduced serum potassium concentration and indicates its value as a guide to therapy when potassium salts are employed.

GUTTMAN, Wilkes-Barre, Pa.

RESPIRATORY FAILURE IN POLIOMYELITIS: A SIMPLE METHOD FOR ITS RECOGNITION AND CONTROL. W. F. STAFFORD JR. and R. GURNEY, Ann. Int. Med. **34**:203 (Jan.) 1951.

The difficulty in recognizing the imminence of respiratory failure and other pulmonary complications in poliomyelitis results in a high mortality rate in this disease. An important contributing factor is failure of the clinician to use the respirator soon enough.

One purpose of this paper is to emphasize an extremely simple method of acquiring objective criteria which are clear-cut indications for use of the respirator. Recognition of impending respiratory failure is readily accomplished by the use of any basal metabolism apparatus capable of measuring vital capacity. With such a machine, a permanent record of the rate and depth of breathing and the maximum possible expiration can be obtained. Swank, by such means, studied the tidal air and vital capacity in five patients with diminished respiratory function, and his findings suggest four stages in the development of respiratory failure: (1) reduction of tidal volume and vital capacity to approximately 350 and 1,000 cc., respectively; (2) the appearance of periodic deep breaths and waxing and waning of the tidal volume; (3) disappearance of the periodic deep breaths; (4) disappearance of waxing and waning of the tidal volume, with further reduction of the tidal volume to approximately 200 cc.

This simple method for the determination of certain aspects of respiratory function which could be used as criteria for the recognition of incipient and advanced respiratory failure seemed especially applicable to patients with poliomyelitis and was utilized by the authors in the cases of five adults with respiratory involvement.

During the test, the patient breathed 100% oxygen in order to prevent hypoxemia. Tracings were made during the early stages of respiratory failure, after total respiratory failure had occurred and the patient was in the respirator, and during the recovery period.

By the use of this method, with repeated respirograms, the authors found it possible to anticipate respiratory failure before it was evident clinically. They emphasize the necessity of measuring vital and minute volumes during artificial respiration. During artificial respiration, pulmonary complications can be demonstrated by this method before any recognizable clinical signs are present. This method also gives a satisfactory indication of return of respiratory function and serves as a guide for evaluation of the patient's ability to withstand removal from the respirator.

ALPERS, Philadelphia.

PHENYLACETYLUREA [PHENACEMIDE] IN THE TREATMENT OF CONVULSIVE SEIZURES. SIDNEY CARTER, DANIEL SCIARRA, and H. HOUSTON MERRITT, Dis. Nerv. System **11**:139 (May) 1950.

None of the common anticonvulsants have been effective against all types of seizures or impressive in the control of psychomotor epilepsy. Toxic side-effects may result from the use of any of them. Phenacemide (Phenurone) has been reported as efficacious in all types of convulsive disease, especially the psychomotor variety, and as having low toxicity for laboratory animals. The authors tested phenacemide in 88 patients, largely persons with epilepsy resistant to other drugs. The daily dose averaged 2.5 gm. Only 63 cases are analyzed; for 25 follow-up data were unreliable or toxic reactions necessitated discontinuation of the therapy. Of 49 patients with grand mal, 22% were benefited, and 78% showed no alteration; of 25 with petit mal, 32% manifested some reduction in the number of attacks, while 68% remained unimproved; of 12 with psychomotor seizures, 17% were better and 83% were unchanged. In no case in the entire series were attacks completely abolished. As an index of patient satisfaction, only 12 of the original 88 subjects have continued to take the compound after 18 months. Of 71 patients in whom side-effects could be evaluated, 44 (62%) had toxic reactions, in 24 of whom they were severe enough to necessitate stopping the drug. Such untoward results were noted as early as one week after prescribing phenacemide and on doses as low as 0.5 gm. daily. In order of frequency, the following side-effects occurred: gastrointestinal disturbances, drowsiness, unsteadiness, liver dysfunction, personality changes, rash, headache, dizziness, fatigue, temperature deviation, leucopenia, and glare phenomenon. The psychological disorders included psychosis, depression, and exaggeration of previous instability. The rather high incidence of possible hepatic damage would seem to make phenacemide an impractical medication because of the need for frequent liver function tests. Leucopenia and injury to the liver are the most alarming of the reactions which developed. It is concluded that, while phenacemide has some anticonvulsant activity, it is not superior to established drugs and that the high percentage of toxic consequences limits its usefulness.

BEATON, Tucson, Ariz.

ELECTROPHRENIC RESPIRATION IN ACUTE BULBAR POLIOMYELITIS: ITS USE IN MANAGEMENT OF RESPIRATORY IRREGULARITIES. S. J. SARNOFF, J. V. MALONEY JR., B. G. FERRIS JR., L. C. SARNOFF, and J. L. WHITTENBERGER, J. A. M. A. **143**:1383 (Aug. 19) 1950.

Acute bulbar poliomyelitis is not infrequently complicated by involvement of the center which drives and coordinates respiration.

The difficulties resulting from involvement of the respiratory center are generally thought to be of two types: (*a*) grossly irregular respiratory rhythm and depth and (*b*) lack of coordination of the muscles of respiration.

Attempts to manage the patient with this type of poliomyelitis in the tank type of respirator of Drinker and Shaw are generally thought to be ineffective when involvement of the respiratory center is severe. This is largely because of the impossibility of substituting the rhythm of the respirator for the patient's grossly irregular "respiratory fibrillation."

In normal, unanesthetized man, electrophrenic respiration by external stimulation causes prompt suppression of spontaneous respiration, an observation confirmed in over 400 instances. The data cited in this paper support the authors' early hope that in the patient with bulbar poliomyelitis all spontaneous respiration, including the respiratory irregularities, would be suppressed, thus permitting one to supply regular, effective respiration. At least one phrenic nerve must be partially or completely uninvolved if this method is to be employed.

It was found that in nine patients with central respiratory irregularities due to bulbar poliomyelitis the irregularities could be suppressed in each case by electrophrenic respiration and regular effective ventilation provided.

The extraordinary extent and severity of central nervous system derangement that can exist and still be reversible if the critical demands of the respiratory and circulatory systems are met have here been demonstrated by Sarnoff and his colleagues. The electrophrenic respirator is not a hazard in the presence of circulatory inadequacy and may actually elevate the blood pressure and cardiac output in this condition.

The electrophrenic respirator consistently and strikingly diminished the restlessness and hypertension in one patient and achieved similar results in others. The mechanisms involved are not known.

It was thought that nursing care was facilitated in the treated group of patients, as compared with that of the usual tank-enclosed patient.

It is not unlikely that the tank respirator, although it may not succeed in achieving control of respiration, may be able to maintain control of respiration once it has been established. One eventual application of electrophrenic respiration may be to adapt the refractory patient to the tank respirator, should it become desirable to do so.

The usefulness of the electrophrenic respirator cannot be considered as established in bulbar poliomyelitis until additional experience has been obtained, according to the authors, but the foregoing data are encouraging.

ALPERS, Philadelphia.

USE OF ERGOT PREPARATIONS IN MIGRAINE. M. FUCHS and L. P. BLUMENTHAL, J. A. M. A. **143**:1462 (Aug. 26) 1950.

It is most commonly stated that no instance of ergotism has occurred in persons receiving ergotamine tartrate for migraine. The introduction of agents with decreased toxicity and the development of medication which can be conveniently self-administered emphasize the need for critical reevaluation of the problem of toxicity.

The authors report two instances of toxic effects following the administration of ergot alkaloids in patients with incontrovertible migraine. They point out that overdosage should be scrupulously avoided. Malnutrition and hypertension are conditions that should lead to further restraint in the use of ergot alkaloids, as brought out by these cases.

ALPERS, Philadelphia.

SPASTIC SPINAL PARALYSIS RESPONDING TO POTASSIUM THERAPY: REPORT OF A CASE. E. BARRETT, J. A. M. A. **145**:138 (Jan. 20) 1951.

There have been many reported cases of muscular weakness and flaccid paralysis in which the condition has responded promptly to treatment with potassium—in particular, cases of familial periodic paralysis and individual cases with similar symptoms. This, it is believed, is the first reported case of spastic paralysis of long duration in which there was a prompt and dramatic response to potassium therapy on repeated courses of treatment.

The patient was a white woman aged 29 with two children aged 1 and 4 years. Three relatives were said to have epilepsy. Her illness had started 11 years before with clumsiness in the knees and stiffness of gait. Various joints were subsequently involved in varying degrees of pain and stiffness. Occasionally there were fibrillations of the muscles of both arms and legs. During each of her pregnancies there was a remission, followed each time by a severe relapse. She did not recover from the last relapse, about one year ago, but became gradually worse.

When seen, she walked with great difficulty, with a characteristic spastic, shuffling gait. On examination, this gait proved to be pseudoparetic, with hyperactive deep reflexes but without true muscular weakness. The Babinski and other pathologic reflexes were absent. The abdominal reflexes were absent. The Romberg sign was slightly positive, but there were no other signs of ataxia. There was no intention tremor. Sensibility was intact. The eyegrounds were normal. The speech was rapid, being neither scanning nor dysarthric. The patient's mental outlook was almost despondent.

Spastic spinal paralysis is merely a syndrome and is present in a large number of diseases of the central nervous system affecting the extrapyramidal pathways in the spinal cord. The most plausible diagnosis in this particular case seems to be the variation of lateral sclerosis reported by Seeligmüller and, later, by Strümpell. The condition is described as a frequently hereditary form, beginning at the age of 20 to 30, or younger, and taking a very slowly progressive course. Its principal, sometimes only, symptoms are spastic, pseudoparalytic gait, for a long time without muscular weakness, and hypertonicity of the deep reflexes. The pathologic lesions in such cases are found to be degenerations in the lateral and anterolateral funiculi of the spinal cord, affecting particularly the extrapyramidal tract, and extending upward through the medullary pyramids, pons, and crus into the internal capsule.

Four courses of potassium nitrate were given, starting at 3 gm. a day in the first course and increasing to 10 gm. a day in the fourth. There were a dramatic response to each course of treatment and a recurrence of symptoms each time the drug was stopped. Between the third and the fourth course the patient was given 10 gm. of L-glutamic acid a day in gelatin capsules. While without treatment her symptoms had promptly recurred, L-glutamic acid retarded this recurrence to some extent.

It was found that the determination of potassium in the blood was an unreliable indicator in regard to therapy. In respect both to pain and to paralysis the final dose of 10 gm. a day yielded the best results.

The observations raise a question whether the spastic spinal paralysis in this case, due to potassium deficiency, is a pathologic condition *sui generis* or whether such an electrolyte imbalance plays a role in other conditions with similar symptoms. The significance of this report would seem to lie in its implications regarding the great number of similar conditions in which there is a pressing need for clarification of etiology and for improvement of treatment.

ALPERS, Philadelphia.

TREATMENT OF HEMOPHILUS INFLUENZAE MENINGITIS WITH CHLORAMPHENICOL AND OTHER ANTIBIOTICS. F. R. MCCRUMB JR., H. E. HALL, J. IMBURG, A. MERIDETH, R. HELMHOLD, J. BASORA Y DEFILLO, and T. E. WOODWARD, J. A. M. A. **145**:469 (Feb. 17) 1951.

McCrumb and his co-workers describe their laboratory findings with chloramphenicol, chlortetracycline (Aureomycin), streptomycin, and oxytetracycline (Terramycin) in experimental Hemophilus influenzae infections in mice. They found that chloramphenicol exerts significant effects in vitro and in vivo against H. influenzae. The experimental results obtained with chlortetracycline and streptomycin were slightly better. Oxytetracycline, likewise, was found to show similar protection in mice.

Twelve children with H. influenzae meningitis, of ages from 5 mo. to 5 yr., were successfully treated with chloramphenicol. The average duration of fever after institution of therapy was 2.3 days. There was rapid improvement of the clinical condition, with return of the sensorium in 1.3 days. There were no fatalities. One of the 12 patients had neurologic residuals, but treatment of this patient was not instituted until the seventh day of the disease.

Chloramphenicol was administered by the oral and rectal routes. The mean duration of treatment of the 12 patients was 8.0 days, and the amount of antibiotic administered was 10.4 gm. Chloramphenicol treatment presented no real problem from the point of view of administration. Five patients received the antibiotic by gavage. The concentration of chloramphenicol in the spinal fluid of five patients averaged 13.2 γ per cubic centimeter, which was roughly one-half the blood level. Toxic manifestations referable to hematologic and renal functions were not observed.

The data obtained on these 12 patients invite further evaluation of chloramphenicol in the treatment of this virulent form of meningitis. Chloramphenicol lends itself aptly to clinical testing because of the relative ease of administration, lack of toxicity, and stability of the compound, making bioassay in various tissues a relatively simple procedure.

ALPERS, Philadelphia.

PROPHYLACTIC AND THERAPEUTIC CONTROL OF VESTIBULAR DISTURBANCES WITH DIMENHYDRINATE. L. N. GAY, J. A. M. A. **145**:712 (March 10) 1951.

Gay had reported previously on the prevention and treatment of seasickness with dimenhydrinate (Dramamine) in a group of 1,366 soldiers. The data accumulated on the voyage proved that dimenhydrinate in doses of 50 to 100 mg. every six hours is a nontoxic, prophylactic, and therapeutic drug capable of controlling the symptoms of seasickness. Of the 389 men who had moderate to violent symptoms of seasickness, complete relief was obtained by all but 17.

Since motion sickness is associated with vestibular imbalance, it was decided to observe the effect of the administration of dimenhydrinate (50 to 100 mg. every four hours) to patients with various types of dizziness of labyrinthine, as well as central, origin.

A total of 63 patients with acute or chronic labyrinthine symptoms were treated. Of these 63 patients with imbalance, 74.6% were greatly improved after taking the drug. Many of the patients had to continue with maintenance doses in order to remain free from dizziness.

The benefits derived from the drug show that dimenhydrinate should be given to all persons with disturbance of balance before recourse to section of the nerve by the neurosurgeon, to destruction of the labyrinth with alcohol injection, or to electrocoagulation by the otologist.

ALPERS, Philadelphia.

TREATMENT OF MYASTHENIA GRAVIS WITH OCTAMETHYLPYROPHOSPHORAMIDE: A PRELIMINARY REPORT. J. A. RIDER, S. SCHULMAN, R. B. RICHTER, H. C. MOELLER, and K. P. DUBOIS, J. A. M. A. **145**:967 (March 31) 1951.

This report deals with the results of the administration of octamethylpyrophosphoramide, a stable and relatively nontoxic anticholinesterase agent, to six consecutive patients with myasthenia gravis. With the exception of the sixth, the patients had moderate to severe myasthenia and were admitted to the hospital because they were dissatisfied with neostigmine therapy or were obtaining poor to indifferent results.

Octamethylpyrophosphoramide has the advantage that two oral doses of 9.5 to 18 mg. a day result in evenly maintained strength, which is generally greater than the maximal strength with neostigmine.

Of the six clinical trials, four were successful. Of the four patients in whom complete replacement of neostigmine was possible, all preferred the new drug because of its smooth and sustained action. These four patients were maintained on administration of octamethylpyrophosphoramide for periods of from one to five months.

The two failures were in patients with severe myasthenia gravis, in whom the response to neostigmine had been poor. Those patients who obtain little benefit from even large amounts of neostigmine will probably get little additional benefit from the new drug.

There is a mutual potentiation of toxic side-effects when neostigmine and octamethylpyrophosphoramide are taken together. Since this is most marked in patients with severe myasthenia gravis, transfer from neostigmine to the new compound in such patients may be difficult, or even impossible.

Serum and red-cell cholinesterase determinations are useful as a guide in regulation of the dose during the period of transfer from neostigmine to octamethylpyrophosphoramide. After the range of the maintenance dose is established, however, minor variations in the requirement of the new compound are not accompanied by changes in blood cholinesterase activity. After withdrawal of octamethylpyrophosphoramide, its therapeutic effect is greatly diminished within 24 hours, but the blood cholinesterase activity rises slowly to normal over a period of more than two months.

Rider and his co-workers found no correlation between the severity of the disease or the neostigmine requirement and the dose of octamethylpyrophosphoramide.

ALPERS, Philadelphia.

RECENT ADVANCES IN TREATMENT OF MIGRAINE. A. P. FRIEDMAN and T. J. C. VON STORCH, J. A. M. A. **145**:1325 (April 28) 1951.

At present, most investigators explain the prodromes, course, symptoms, signs, and sequelae of migraine on the basis of changes in the cerebral and meningeal circulation. There are other, more basic, and at present unknown, factors which alter the circulation. The importance of psychologic factors in migraine has long been recognized.

The authors have been able to observe a group of 604 patients with migraine for a period of one to four years. In this report the emphasis has been placed on the evaluation of various pharmacologic agents and of psychotherapy.

The authors conclude that the treatment of migraine is a complex, individualized procedure. Symptomatic treatment is essentially one of pharmacotherapy, and the best results have been

obtained with the use of the ergotamine derivatives, notably, ergotamine with caffeine (Cafergot). Prevention of an attack is best accomplished by psychotherapy. However, the use of certain sympatholytic drugs holds promise.

In the treatment of migraine, the frequency and severity of the patient's headaches can now be favorably modified.

ALPERS, Philadelphia.

EVALUATION OF RED CROSS GAMMA GLOBULIN AS A PROPHYLACTIC AGENT FOR POLIOMYELITIS: 1. PLAN OF CONTROLLED FIELD TESTS AND RESULTS OF 1951 PILOT STUDY IN UTAH. W. McD. HAMMON, L. L. CORIELL, and J. STOKES JR., J. A. M. A. **150**:739 (Oct. 25) 1952.

The principal purpose of the experiment described in this, and in the subsequent, paper of the series was to determine whether gamma globulin, as prepared for and furnished by the American National Red Cross for measles prophylaxis, would protect against the paralytic manifestations of poliomyelitis when administered in reasonable dosage before the onset of illness. A secondary purpose was to determine, if protection were afforded, the duration of protection in the dosage selected for the experiment. Another secondary purpose was to determine whether gamma globulin would permit or interfere with inapparent or milder types of nonparalyzing clinical infection and the subsequent development of active immunity.

Hammon and his colleagues conducted a pilot study during an epidemic in Utah in September, 1951, during which 5,767 children received injections. By a method of random selection, half the children in the study received injections of gamma globulin, and the other half, injections of a gelatin solution. No significant clinical reactions of any type were observed. There was no evidence that the inoculations led to any increase or localization of paralysis.

As anticipated, the number of cases of poliomyelitis occurring in the group receiving injections was too small to permit the authors to determine whether gamma globulin had afforded any protection.

ALPERS, Philadelphia.

EVALUATION OF RED CROSS GAMMA GLOBULIN AS A PROPHYLACTIC AGENT FOR POLIOMYELITIS: 2. CONDUCT AND EARLY FOLLOW-UP OF 1952 TEXAS AND IOWA-NEBRASKA STUDIES. W. McD. HAMMON, L. L. CORIELL, and J. STOKES JR., J. A. M. A. **150**:750 (Oct. 25) 1952.

In July, 1952, injections of either Red Cross gamma globulin or gelatin were given to 33,137 children, of ages from 1 through 6 years, in Harris County, Texas, and 15,686 children, of ages from 2 through 11 years, in Woodbury County, Iowa, and Dakota County, Nebraska. The epidemics selected have continued in such a manner that 85 cases have occurred already in the inoculated group, and cases continue to occur. It would appear that the number of cases developing will be large enough to give highly significant findings.

ALPERS, Philadelphia.

EVALUATION OF RED CROSS GAMMA GLOBULIN AS A PROPHYLACTIC AGENT FOR POLIOMYELITIS: 3. PRELIMINARY REPORT OF RESULTS BASED ON CLINICAL DIAGNOSIS. W. McD. HAMMON, L. L. CORIELL, P. F. WEHRLE, and others, J. A. M. A. **150**:757 (Oct. 25) 1952.

In the preceding series of three controlled field tests to evaluate the prophylactic effect of Red Cross gamma globulin in poliomyelitis, 54,772 children, between the ages of 1 and 11 years, were inoculated, one-half of them with gamma globulin and one-half with a solution of gelatin. These three field tests were conducted in areas that were experiencing severe epidemics of poliomyelitis. The injections were given to apparently normal, healthy children living in the area, with the full understanding, permission, and cooperation of the parents. Which of the two materials any one child had received was unknown to all—children, parents, and investigators—until completion of a follow-up period considered to be adequate for determining a final diagnosis.

A preliminary tabulation of results as of Oct. 1, 1952, shows that paralytic poliomyelitis had been diagnosed in 90 cases in the study group. Analysis of these patients on the basis of the type of injection received shows that significant protection was conferred by the gamma globulin.

During the first week after injection there was no significant reduction in the number of cases in the group receiving gamma globulin, but the severity of paralysis appears to have been modified. From the second through the fifth week highly significant protection was demonstrated. After the fifth week this was less evident, but more definite conclusions regarding the duration of protection and possible modification of the disease will be available after a longer follow-up period. Laboratory studies, still incomplete, should give information regarding the effect of gamma globulin on inapparent injection and the subsequent development of active immunity.

ALPERS, Philadelphia.

Muscular System

THE ANTERIOR TIBIAL SYNDROME. A. BARHAM CARTER, R. L. RICHARDS, and R. B. ZACHARY, Lancet **2**:928 (Nov. 19) 1949.

The authors report nine cases of the anterior tibial syndrome. The cases were divided into two groups according to their clinical features. In the first group, consisting of seven cases, the initial symptom was pain in the leg while the patient was playing football, followed by swelling over the anterior tibial compartment, the classic signs of inflammation, and, later, inability to dorsiflex the foot and toes. The second group consisted of two cases in which transfusions had been given into the veins of the leg. Within a short time after the transfusion both patients complained of pain in the front of the leg into which the transfusion had been given and were later found to have paralysis of the anterior tibial muscles.

The paralysis affected chiefly the muscles of the anterior tibial compartment—the tibialis anterior, the extensor digitorum longus, and the extensor hallucis longus. The consistency of the affected muscles was described as "woody" or "indurated." In six cases there was sensory disturbances in the distribution of the anterior tibial nerve. In seven cases the extensor digitorum brevis, supplied by the anterior tibial nerve, was affected. The authors summarize their views on the pathogenesis of this condition as follows:

Sudden and unaccustomed use of the pretibial muscles in untrained men traumatizes the muscles, so that, as the result of the rupture of a few muscle fibers or of hemorrhage into the muscle, the swelling of the muscles that normally accompanies exertion is exaggerated; this produces tension within the rigid anterior tibial compartment sufficient to impede the circulation to the muscles and leads to ischemic necrosis.

In treatment, the authors advise, first, prophylaxis by suitable graduated training. When the condition is recognized early, rest in bed with the limb elevated and the foot splinted in the neutral position is prescribed. Once paralysis has developed, surgical decompression of the muscles should be undertaken as an emergency.

MADOW, Philadelphia.

STEINERT'S DISEASE: SPECIAL ATTENTION TO THE PROBLEM OF CATARACT. E. AZZI, Arq. neuro-psiquiat. **9**:1 (March) 1951.

Siblings with dystrophia myotonica, or Steinert's disease, were studied with other members of their families. One of the patients presented a picture of Thomsen's disease, and 13 years later dystrophia myotonica (myotonia atrophica), with incipient cataract, bilateral ptosis, defective extraocular and mimetic musculature, atrophy of distal muscles with foot drop, and testicular atrophy with impotence, developed. In the second sibling pair, a woman with a typical syndrome had a brother four years older with the same disease. Small cysts were found in her ovaries at operation. In the man the disease was more advanced, with repeated attacks of myocardial insufficiency, due probably to involvement of heart muscle. In the third sibling pair, the younger one had a less advanced form of the disease, with early atrophy of the distal parts of the extremities and definitive myotonia, but no dysendocrinism. There were numerous cases of cataract in the collateral and direct descendants in this family.

Hoffmann was the first to point out (1904) the relation of cataract to this disease. Cataract is more important than other ocular complications because it may be the presenting symptom of the malady and may occur without any of the other characteristic signs. The author states that cataract is present in 100% of the cases of dystrophia myotonia if the slit lamp is used for diagnosis. It is found in members of the families in which dystrophia myotonica is present

without other evidence of the disease. Azzi describes the coexistence of the Vogt variety of cataract—multicolored punctiform clouding in the anterior and posterior cortices—and dystrophia myotonica. It is difficult to identify this cataract with that due to parathyroid dysfunction. The author prefers to consider that cataract in this disease is due to diencephalic dysfunction. The absence of cataract in Thomsen's disease does not stamp it as a separate clinical entity. The later appearance of features of dystrophica myotonica in a case at first considered one of Thomsen's disease is cogent evidence for the latter disease being an earlier variant of the full-blown syndrome.

N. Savitsky, New York.

Treatment of Myasthenia Gravis: Denervation of the Carotid Sinus in Three Cases. D. Furtado and Filipe da Costa, Arq. neuro-psiquiat. **9**:103 (June) 1951.

Denervation of the carotid sinus was first attempted in myasthenia gravis by Thevenard and Leger in 1943. The denervation causes hyperplasia of the adrenal glands. Improvement may appear immediately or after an interval. Neostigmine therapy should not be dropped before or immediately after the operation, and it is wiser to increase the dose before the operation. Three cases are reported in which the carotid sinus was denervated. In two cases the results were good. In one case the myasthenic symptoms disappeared for three months. In addition to the denervation of the carotid sinus in all the reported cases, the sympathetic nerves around the carotid artery were also cut. The improvement is explained by the stimulation of circulation of the hypophysis, which, in turn, has a salutary effect on adrenal function.

N. Savitsky, New York.

Encephalography, Ventriculography and Roentgenography

Acromegaly and Contrasting Conditions: Notes on Roentgenography of the Skull. S. Moore, Am. J. Roentgenol. **68**:565, 1952.

Moore investigated the incidence and other aspects of metabolic craniopathy on the basis of 10,000 roentgenograms of the skull. Twelve films presented some of the roentgenologic characteristics of acromegaly in addition to the hyperostosis of the skull. The question then arose whether the patients had hyperostosis or whether the thickening of the vault was simply a feature of the acromegaly. In 6 of the 12 cases a clinical diagnosis of acromegaly had also been made. In the other six cases the diagnosis was made on the basis of the x-ray findings in the skull films. When the 10,000 examinations were reviewed, it was found that on the basis of the skull films 24 males could be considered to have acromegaly. Three males could not definitely be considered to have acromegaly but presented sufficient x-ray evidence to be classified as acromegaloid. One male had acromegaly associated with hyperostosis. For 18 females there was an x-ray diagnosis of acromegaly; 3 were considered acromegaloid, and 5 had acromegaly associated with hyperostosis.

From the study of roentgenograms of the skulls of the patients with acromegaly and the patients with hyperostosis, from a study of roentgenograms of the skull of normal persons, and from a study of anatomic specimens, Moore draws the following conclusions: 1. Acromegaly and metabolic craniopathy are both constitutional conditions. 2. In hyperostosis the skull only is involved, and the cranial cavity becomes smaller because of the thickening of the skull. 3. The vault of the skull is not thickened in acromegaly; it is usually thin. 4. The sella turcica is not necessarily enlarged in acromegaly and is not enlarged at all in hyperostosis. 5. Metabolic craniopathy occurs 98 to 100 times as frequently in women as in men. Acromegaly is generally considered to occur with about equal frequency in the two sexes, but in this series there were 24 males and 18 females.

Weiland, Grove City, Pa.

News and Comment

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Gulbrandsen, Halbert, Denver
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Mock, John Edward, Philadelphia
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Moore, William Thomas, Norristown, Pa.
Morgan, Norman Charles, Warren, Pa.
Morrow, John Tarlton, Jr., Pittsburgh
Naftalin, Moses, New York
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Newbury, Constance Lincoln, Pittsburgh
Nichols, Florence Lilian, Philadelphia
Nord, Charles Lowell, Ann Arbor, Mich.
Osher, Stanley, Oakland, Calif.
Peteler, Jennings C. L., Minneapolis
Pfeffer, Burton B., New York
Prunier, J. Edward L., Worcester, Mass.
Rath, Frederick, West Brentwood, N. Y.
Regan, Joseph James, St. Petersburg, Fla.
Reiss, Harry, Ossining, N. Y.
Rhead, Clifton Charles, Jr., Chicago
Richman, Abraham Arnold, Brooklyn
Rizzo, Nicholas Daniel, Boston
Rosen, Irving M., Dorchester, Mass.
Rubin, Isaiah, Aaron, New York
Rudo, Marvin, Perry Point, Md.
Russ, Zack, Jr., Schenectady, N. Y.
Ruttenberg, Bertram Aaron, Philadelphia
Schneidmuhl, Abraham Moses, Baltimore
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Sims, Henry Mitchell, Fort Smith, Ark.
Socarides, Charles William, New Castle, Del.
Stauffer, Tom G., Scarsdale, N. Y.
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Toolan, James Michael, New York
Trench, James McKechan, Hartford, Conn.
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Wood, Alfred Conard, Jr., Philadelphia
Wylie, Howard Lee, Worcester, Mass.
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NEUROLOGY

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Jarrett, Paul S., Miami, Fla.
Krieger, Howard Paul, Hewlett, N. Y.
Ladwig, Harold Allen, Omaha
Lesse, Stanley, New York
Lloyd, Leslie Gerard, Long Beach, Calif.
Paddison, Richard Milton, Haddonfield, N. J.
*Robins, Alvin L., Bethesda, Md.
Sprofkin, Bertram Edward, Nashville, Tenn.
Van Buskirk, Charles, Minneapolis
Victor, Maurice, Boston
Watson, Charles Wesley, West Newton, Mass.
*Wright, George J., Jr., Pittsburgh
*Youngue, Eugene L., Jr., Pittsburgh

PSYCHIATRY AND NEUROLOGY

Dillon, Harold, Philadelphia
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AMERICAN LEAGUE AGAINST EPILEPSY

The American League Against Epilepsy announces the Jerry Price Memorial Prizes, with a total value of $1,000, contributed jointly by Mr. and Mrs. Fred Markham and the League, for dissertations on epilepsy.

Cash awards comprise first, second, and third prizes of $500, $200, and $100, respectively. There are book prizes for other contestants and possible publication of one or more contributions in the journal *Epilepsia*.

The contest is open to the students of any approved medical school in the United States or Canada. Any one of the many aspects of epilepsy may be covered. Essays should be original, typed double-spaced, and preferably no more than 5,000 words in length.

Contributions should be mailed before Aug. 1, 1954, to Dr. J. K. Merlis, Secretary, American League Against Epilepsy, 150 S. Huntington Ave., Boston 30.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC.

At the December, 1953, meeting the officers and directors of the American Board of Psychiatry and Neurology, Inc., chose the following dates and places for the examinations for certification in Psychiatry and/or Neurology to be given by this board: Dec. 13 and 14, 1954, New York; Feb. 28 and March 1, 1955, New Orleans; mid-October, 1955, San Francisco, and December, 1955, New York.

DR. WARTENBERG ACCEPTS GUEST PROFESSORSHIP

Prof. Robert Wartenberg, of the University of California Medical School at San Francisco, has accepted a guest professorship at Freiburg University for six months beginning in April, 1954.

AMERICAN ACADEMY FOR CEREBRAL PALSY

The eighth annual meeting of the American Academy for Cerebral Palsy will be held Nov. 5-7, 1954, in Williamsburg, Va., at the Williamsburg Inn.

Books

The Sensory Order. An Inquiry into the Foundations of Theoretical Psychology. By F. A. Hayek, with an introduction by H. Klüver. Price, $5.00. Pp. 209. University of Chicago Press, 58th St. and Ellis Ave., Chicago 37, 1952.

"An economist ventures," in the author's own introductory words, "to rush in where psychologists fear to tread," and a prominent psychophysiologist introduces the venture as "one of the most interesting and significant books . . . during the last decades." The touch of originality is maintained by the revelation that the treatise goes back to a draft the author wrote as a student some thirty years ago. To the correct answers given then he feels he has at last found some pertinent questions. His hold on posterity may be strongest with this interlude between works which have established his contemporary reputation as an economist.

An outsider's claim for competence in an alien field must rest on his scholarly acquaintance with it, fortified by that detached insight which the shortsighted expert may lack. The book fulfils both these conditions.

Theoretical considerations of the sort implied by the title are apt to put off many a medical reader. Not only does the author shun the hardships of philosophical writing, but he also has learned to dread ruminations about the old uneasy riddles with their old uneasy answers. But this book may do two things for us: first, to see the problem of brain and mind in a new light; second, to explain how far this relationship can be explored and why explanation will go no further than certain generalities.

Hayek's argument runs like this: Traditional psychophysiology explains our experiences as an aggregate and elaboration of primary sensations. Experiences are usually held to be structures built from the bricks picked up by single and simple receptors which respond to appropriate single and simple stimuli; these remain virtually unaltered from the periphery to the center. This explanation is based on the naïve assumption that the features of the physical world are mirrored in a one-to-one relationship by the arrangements of the nervous system. Modern physics and biology have made such an assumption untenable, quite apart from the fact that an idealistic philosophy has always opposed this view. The phenomenal world is not the physical world, and what we perceive is not a mere taking hold of physical qualities; it always is an interpretation.

One may add here that words like "grasp," "apprehension," "comprehension," and "perception" are metaphors taken from the tactile sphere; they do not account for the transformation of the material "seized," or for the long circuitous way this has to go before it is reconstructed and eventually projected back into the physical world. Perception happens in a flash of time, it is true. Yet, how much more does this transformation apply to perception, or "food for thought," than it does to the process of actual nutrition! The simple nutrients, we grant, are broken down and altered beyond recognition as soon as they are taken in, to reappear as our own flesh and blood only after innumerable intricate metabolic steps.

Hayek goes further than postulating such transformation by the senses. The basis of sensation is discrimination, and discrimination is between at least two things. A simple stimulus would be utterly meaningless to organisms were it not for the relation it has to at least one other stimulus. That stimulus may be long past, almost present, or both. All sensation, therefore, implies a relationship; it is not about absolute qualities, but about similarities or differences between qualities; it rests on relative values. Mind, the total of sensations, is, consequently, a complex not of things or qualities, but of relations.

As no sensation can occur without its own past, to which it must be related, all sensation is an interpretation based on learning. Now learning means to establish relationships, to create order out of chaos. This process begins with inception of all phylogenetic and ontogenetic growth. Connections between neurons are established on the grounds of events occurring together in the time and/or space. Discrimination is conceivable only if events are being arranged in an orderly fashion, i. e., classified into groups or falling into classes.

Here, then, is the main thesis: Mind is an instrument of classification, and sensations are classified relationships between events. "By 'classification' we shall mean a process in which on each occasion on which a certain recurring event happens, it produces the same specific effect, and where the effects produced by one kind of such events may be either the same or different from those which any other kind of event produces."

This sounds like a very dry manner of accounting for the freshness of immediate experience. But there is no reason to believe that the philosopher's or scientist's analysis and categorizing is a mechanism essentially different from his mental activity when he was a child playing with, say, a red ball, the size of an orange. In order to see it as such, the child must have had previous experience with roughness and smoothness, bounciness, redness, and orange size. Although perhaps not able to use all these terms, it must have developed the relevant sensory mechanisms, separating them as experiences accumulated, by way of differentiation. Differentiation is the classifying of and by neural pathways. Finally, the child forms a class under which all identical red balls, or the "same" ball on subsequent occasions, have to be subsumed, and from which all different-looking ones must be excluded. How much different they have to look for noninclusion depends on the child's discrimination, again a function of the ability to classify.

We see the close ties which ally the author to the thought of Coghill, Lashley, and Hebb; of Craig, Wiener, Russell, and Korzybski, and the gestalt school. The essential endeavor and difficulty of thinkers on the body-mind problem seems to be that of merging the two meanings of the term "structure." This is used in a physical (anatomical) sense for objects such as the brain, and in a logical sense for systems of abstracts. It is Hayek's merit to show that the two meanings can be merged in the larger concept of "classification." The function of sensory nerve structures and of the mind is to classify.

The main anatomical feature of the nervous system is its tree-like arrangement. A stem with branches implies a hierarchical set-up. Herein lies an old conceptual danger of which Hayek has not quite freed himself when he speaks, with Hughlings Jackson and Penfield, of a "highest and most comprehensive centre," and of the way a commanding general functions with regard to his army. It is, on the contrary, characteristic of classifications, and the inescapable conclusion of "the sensory order," that we are never dealing with one principle and one hierarchy alone, but with many overlapping each other. Just the same overlap characterizes the anatomical pattern of the nervous system, and there is more rather than less of it, the "higher" the levels which we approach. It is this very overlap caused by converging and diverging pathways (with direct interaction between cell membranes possibly added), it is this constant "interference" pattern between classes of neurons, which seem to enable our thought to be rich as well as precise.

A sensation experienced is always an object perceived. Not only does it belong to a class of similar past objects—and this is its denotation or intrinsic definition—but it also contains a complex of qualities or classes—and this is its connotation or intrinsic definition. A stimulus producing a primary impulse, or more likely a number of them, habitually summons a "following" of secondary impulses, and so on to tertiary impulses, etc. Having a particular effect in common, they become "signs" or "symbols" representing classes, and classes of classes. Not only their kind, but also their degree or size, is classified according to the relation or differences between them. Abstract and concrete become inseparable.

Consequently, "qualities of mental events need not be localized in any particular part of the cortex," although they depend "on their position in the whole network of connexions" and not "on any property of impulses."

The process of emotion is not excluded from this interpretation. Affective qualities find their place along with sensory ones. As they pertain to events occurring both in the exterior and in the interior environment, but more so in the latter, they may not refer to particular points in space. Emotions are more allied to the temporality of events and to their increment and decrement; to the experience of absence and presence, and hence to negation and affirmation, or refusal and acceptance. Hayek sees them as a subsystem and an additional dimension of the mental order, contributing to and modifying differences between sensory modalities and between behavioral attitudes.

Tradition has put the "passions" in a category apart from calm sensory experience and reasoning, and the tendency persists to allot them a special system in the nervous organization. In their crude form they appear to run along phylogenetically old and "primitive" pathways of visceroautonomic-hormonal release and rather short sensorimotor circuits. Emotional storms, whether or not observable by the onlookers, are indeed a crude form of reacting by one who seems to "forget himself," i. e., how to deal with a situation along the rational lines he has "learned." "Refined" and "noble" feelings, on the other hand, and especially those allied to social conventions, are indistinguishable from contemplative and becalmed mental activity.

Learning, seen as a process of reclassification and acquisition of new discriminations, gives Hayek's theory its dynamic aspect. In this view mind and consciousness are a product of experience rather than, as in the older conception, finished tools always ready to seize "given sense data." The photographic plate and the sound recorder, as well as the file cabinet, are commonly envisaged as examples. Such tools are indeed classifiers, but of a passive, rigid, and isolated kind. They sort out, abstract, and process certain aspects, but never the real properties, from the environment. They construct a model on the basis of some structural equivalence. Electronic computors do this even more subtly, but they either are set once for all or at least behave in a predestined way. This they do more than animal "machines," built with the greater freedom due to the large molecules of their protoplasm. Man likewise obeys the laws of chemistry and physics; in addition, he displays the generic features of lower animals. On all these levels his reactions are "abstractions" similar to the reactions of dead objects and primitive organisms. It is his almost infinite ability for rearranging classes and the relations between classes which leads to conceptual thought and ethical behavior. Conversely, insufficient discrimination, i. e., inefficient classification, is the basis of error, prejudice, amoral behavior, neurosis, confusion, and dream experience. To get one's classifications too wide or too narrow, to have one's percepts and concepts fall into the wrong category, is the root of psychopathological reactions. Here lie an important development of Freudian symbolism and the widest applications to practical psychology.

"Knowing," whether in animals, infants or learned men, is a patent or latent reaction based on "theories." "All 'experience' can do is to change these theories." To prove these views, Hayek advocates experiments designed to show that new, and not just better, discriminations, can be learned in sensory fields, hitherto thought to consist of fixed sense data. It should also be possible, in learning-experiments, to interpret in different ways identical stimuli, proceeding on identical primary pathways. As an everyday example, he gives the learning of a language which is not phonetically spelled; identical symbols are given different values according to their combination with other symbols, while other groups of symbols, though differing between one another, become equivalent.

By now we begin to wonder how far we have traveled from physiological materialism to philosophical idealism. The classes of the sensory order are not identical with the attributes of physical events. About these we learn something different through the classifications which scientific method makes. Physical attributes are inferred and communicable first through the transformation by the nervous system, and second, by the translation into a social language. But Hayek occupies a middle position between extreme dualism and positivism, a position which might be called a "radical conciliation." His theory manages to bring about a compromise between gestalt and associationism, on his own terms. How does he handle the crucial problem of "memory"? Classification and order, naturally a happy device when we are confronted with the problem of finding things. The difficulty consists in accounting for "storage," "finding," and "things." How are we going to have mind neither too rigid nor too fluid?

Hayek speaks of "linkages" based on neuronal "followings," linkages which are "presensory" before we can speak of conscious experience. The neuronal connections form as a "semipermanent 'map,'" along the lines of which runs the more fluid "model" of outside events. The "map" is envisaged as a static structural residue laid down by past dynamic or functional "models," but subject to further change by successive models, i. e., *kinds* of stimuli. Relations between models, and models within models, give rise to new models, and so account for an almost unending capacity for classifying.

In his last chapter the author sets the limits to which his or any explanation of mind can go. The concept of the "model" has its limitations; it implies a reference to the phenomenon which it is meant to reproduce; it presupposes a knowledge of that phenomenon. "Explanation"

is model building; it is itself one of the processes which the theory intends to explain. It can, therefore, never reach further than giving an outline of the class or principle to which a phenomenon belongs; it will not predict all the particular phenomena belonging to that class. Explanations are always explanations of principles, not of particulars. Not only must a sorting or calculating machine have the ability to perform an infinitely greater number of "explanatory" operations than the number given by the highest numeral with which it deals; it will also be unable to include its own working in its "explanatory" activity. The brain as a calculating machine, i. e., as seen by the crude materialist, cannot classify or explain each act of its own activity; to do this another brain of greater complexity would be needed. The theory can thus explain the *kind* of physical events by which mental events are produced. But there always is an upper layer of mental events which remain unexplained and "mental" in their own right. "Free will," for instance, is a subjective experience of freedom and can therefore neither be denied nor asserted scientifically. Experience is well enough founded in what we can understand through science. But it is only so founded and can never be completely built up. Nor can psychology "bridge the gap between the realm of the mental and of the physical."

Considering that the nervous system is part of the physical world, an account of the latter is not complete without a full classification, definition, description, and explanation of mental activity. As this is not forthcoming, a full understanding of the physical world must, like an infinite regress, forever elude us, for we ourselves have to do the classifying, defining, describing, and explaining.

In other words, we cannot pull ourselves up on our own bootstraps or occupy a lookout outside the universe.

My liking for the book has led me to intersperse this précis with a few turns of my own thought; for these I must ask the indulgence of the author and of the reader, whom I herewith refer back to the book.

Psychosomatic Approach to Gynecology and Obstetrics. By Fritz Wengraf, M.D. Price $6.75. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill. Pp. 346, with no illustrations.

This volume is publication Number 164 of the Bannerstone Division of American Lecturers in Gynecology and Obstetrics, edited by Dr. E. C. Hamblen, of Duke University School of Medicine.

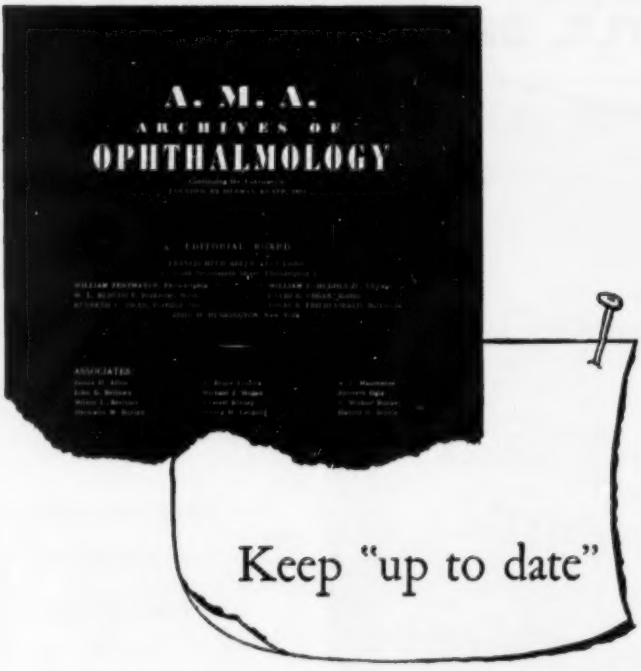
Dr. Fritz Wengraf is adjunct neuropsychiatrist, Beth Israel Hospital, New York, and has had training in both psychiatry and obstetrics and gynecology.

The author presents the psychological and psychiatric aspects of all female generative functions and emphasizes the different reactions of well-adjusted and emotionally disturbed women to their feminine functions. The constructive results of psychiatric support in gynecological and obstetrical situations are illustrated with case histories.

One of Dr. Wengraf's basic premises is that many gynecological disorders are expressions of inner conflicts arising from the patient's personality development and constitutional and hereditary factors.

"The gynecologist" he writes, "must enrich his armamentarium, not with new machines but with a new approach. He must learn to treat his patients by psychological means, not as a substitute for other means but as an addition to and an expansion of his present techniques."

This monograph is encyclopedic in scope and has an extensive bibliography.



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